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The aim of the journal is to convey scientific developments and to create a dynamic discussion platform about pulmonary diseases. With this intent, the journal accepts articles from all related scientific areas that address adult and pediatric pulmonary diseases, as well as thoracic imaging, environmental and occupational disorders, intensive care, sleep disorders and thoracic surgery. Clinical and research articles, reviews, statements of agreement or disagreement on controversial issues, national and international consensus reports, abstracts and comments of important international articles, interesting case reports, writings related to clinical and practical applications, letters to the editor, and editorials are accepted.

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INFORMATION FOR THE AUTHORS

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2 Drafting the work or revising it critically for important intellectual content; AND
3 Final approval of the version to be published; AND
4 Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

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Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Methods, Results, and Discussion subheadings. Please check Table 1 for the limitations for Original Articles.

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Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

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Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	35	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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EDITORIAL

See article: Öztürk B, Kosku H, Güven İ, et al. A Study Examining Compliance with the Anti-Tobacco Law Nb. 4207 Inside Taxis. Turk Thorac J 2017;18:88-93.

Can we Protect the Society from Passive Smoking?

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Similar to active smoking, the inhalation of tobacco smoke, in other words second-hand smoking, causes health problems (1). Therefore, one of the main components in tobacco control is to protect the society from the passive effects of smoking (2). In articles under Law No. 4207, which constitutes a basis for the action plan in national tobacco control, there are regulations that aim to protect the society from the hazards of passive smoking (3). Despite these regulations, some studies have shown that the rates of violation are high.

In one such study, the rate of violation in the prohibition of tobacco use in indoor places has been reported to be 32% in İzmir (4).

Moreover, the use of tobacco and tobacco products is banned in public transport vehicles and taxis under Law No. 4207 (5). However, some studies have revealed that this prohibition is also violated in taxis and enclosed places. A study investigating the knowledge level of taxi drivers on this issue has demonstrated that the awareness of drivers is unsatisfactory and that support for this ban is low (6).

This issue of the journal includes a research study that evaluated whether there was obedience to the smoking ban in taxis under Law No. 4207. In the study by Burcu Öztürk et al., violations in taxis were observed from the outside at intersections with heavy traffic in Ankara and the rate of violation was found to be 2.6% (7). Despite the fact that these observations were made on the move and at specific points, the rate is high. In fact, this rate of violation can be considered to be higher.

To inform the whole society, particularly taxi owners and drivers, on the harms of passive smoking and obedience to the law and to increase the efficiency of inspections will contribute to the reduction in violations.

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7 Öztürk B, Kosku H, Güven İ, et al. A Study Examining Compliance with the Anti-Tobacco Law Nb. 4207 Inside Taxis. Turk Thorac J 2017;18:88-93.

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REVIEW

Treatment After First-Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Resistance in Non-Small-Cell Lung Cancer

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Abstract

Systemic treatment is the basic treatment approach to advanced-stage non-small-cell lung cancer (NSCLC), and chemotherapy and targeted treatments are commonly employed in these patients. Recently, positive results achieved with immunotherapy have led to a growing number of treatment options and prolonged survival time. Today, specific tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, and afatinib, which target the epidermal growth factor receptor (EGFR), and the TKI crizotinib, which targets anaplastic lymphoma kinase gene rearrangement, have become the standard treatment among targeted therapies for patients with sensitive molecular anomalies. However, resistance develops against all these agents after a while. Numerous genetic mutations, T790M+ in particular, have been identified as resistance mechanisms against EGFR-TKIs, and researchers are developing specific inhibitors against them. Among those inhibitors, third-generation EGFR-TKIs such as osimertinib and rociletinib have gained prominence due to their high level of effectiveness and low toxicity profile. Besides, systemic chemotherapy and immunotherapy are proper alternatives. A second biopsy during the progression stage and better clarification of the mechanisms causing secondary resistance will enable more successful treatments in the future.

KEYWORDS: Epidermal growth factor receptor, tyrosine kinase inhibitors, resistance, non-small-cell lung cancer

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INTRODUCTION

Lung cancer is still the primary cause of cancer-related death for both sexes worldwide, causing approximately 1.4 million deaths every year [1]. Non-small-cell lung cancer (NSCLC) cases comprise approximately 80%-85% of all lung cancers. More than half of the NSCLC cases are advanced-stage at the time of diagnosis, and those patients are characterized by poor prognosis. Systemic chemotherapy has long been employed as the primary treatment approach for advanced-stage NSCLC. Despite a series of advances in chemotherapy and the application of histology-based approaches in the course of time, median survival time does not exceed 1 year [2]. On the other hand, recent discoveries of somatic mutations in NSCLC and the employment of specific inhibitors against them have led to significant changes in the treatment of advanced-stage NSCLC. Currently, there are two key oncogenic molecular anomalies reflected in routine practice: epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase gene rearrangement.

Epidermal growth factor receptor mutations are observed in approximately 10% of the whole patient group, whereas this rate may go up to 40% among Asians, non-smokers, and in patients who have adenocarcinoma histology. Deletion at exon 19 and point mutation at exon 21 (L858R) are the most common EGFR mutations [3]. The presence of these mutations indicates sensitivity to EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, and afatinib. The use of erlotinib and gefitinib (first-generation TKIs) and afatinib (second-generation TKIs) in first-, second-, and third-line of treatment in patients with sensitive EGFR mutations has delivered significant survival advantages, and it has become a popular treatment option commonly preferred in routine daily practice (Table 1).

Although remarkable results have been achieved with first-/second-generation EGFR-TKIs, median progression-free survival (PFS) times do not exceed 10-12 months-that is, we encounter acquired resistance after a while [4]. Numerous genetic mutations have been identified as resistance mechanisms, and specific inhibitors are being developed against them. We aim to review resistance mechanisms against first-/second-generation EGFR-TKIs and evaluate potential approaches to overcome this resistance and next-generation EGFR-TKI agents.

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Table 1. EGFR-TKIs

First-generation (reversible) TKIs
- Erlotinib, gefitinib
Second-generation (irreversible) TKIs
- Afatinib, dacomitinib, neratinib
Third-generation TKIs
- AZD9291 (osimertinib), CO-1686 (rociletinib), HM61713, EGF816X, ASP8273

EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor

Table 2. Secondary resistance mechanisms to first/second-generation TKIs

Secondary mutations of the driver oncogene
- T790M+ at exon 20
Activation of other signaling pathways
- Activation of downstream signaling pathways
• BRAF or PIK3CA mutation
- Activation of parallel signaling pathways
• MET, HER-2, and FGFR activation
- Histological transformation
• Epithelial-mesenchymal transition
• As a recourse to the small-cell-type
- Clonal heterogeneity

TKI: tyrosine kinase inhibitor

EGFR-TKI RESISTANCE AND APPROACHES TO OVERCOMING THE RESISTANCE

EGFR-TKI Resistance Mechanisms

Acquired resistance refers to disease progression after response to EGFR-TKI treatment [5,6]. It has been reported to occur mainly via two methods. The first includes secondary mutations of the driver oncogene, and the second is identified as the activation of bypass signal pathways other than the EGFR pathway [5,7,8]. The T790M gatekeeper point mutation at exon 20 is reported to be the most frequently observed (accounting for approximately 50%-60% of all causes) secondary mutation of the driver oncogene [8,9]. As for the activation of other signaling pathways that continue the carcinogenesis process by bypassing the EGFR pathway, identified primary resistance mechanisms include the activation of downstream signaling pathways such as BRAF (1%) or PIK3CA (2%) [10]; activation of parallel signaling pathways such as c-MET (5%), HER-2 (8%-13%), and FGFR [11,12]; epithelial-mesenchymal transition (6%) or histological transformation manifesting as a recourse to the small-cell type [13]; and clonal heterogeneity [5,7,14,15]. Since acquired resistance mechanisms present such a broad range, a re-biopsy during the progression stage is of key importance to reveal resistance mechanisms (Table 2) [5,16].

Approaches to Overcoming EGFR-TKI Resistance

While deciding on treatment options for a patient progressed during EGFR-TKI treatment, we need to identify the type of progression [5,7]. In this manner, two types of progression have been described: oligoprogression and systemic progression. In oligoprogression, the primary tumor is under control and the disease progresses slowly and includes few intracranial or extracranial asymptomatic metastases. Usually, lesions with limited progression are subjected to a stereotactic ablative radiotherapy and TKI treatment is maintained, which is considered a proper approach in such cases [7]. In systemic progression, however, other treatment alternatives, particularly systemic treatment, are recommended.

Transition to Chemotherapy

Chemotherapy is the most preferred method available today. As quite a large portion of EGFR mutations is observed in adenocarcinoma, pemetrexed is presented as a frequently used chemotherapeutic agent. A non-randomized retrospective study compared single-agent pemetrexed with platinum-based combination chemotherapy and reported that pemetrexed resulted in better PFS [17].

Continuation of EGFR-TKI

Clinical observations indicating that up to 23% of patients undergo rapid progression after the discontinuation of EGFR-TKIs have led to an approach that involves the continuation of TKI treatment [18]. In the ASPIRATION study (phase II) conducted on the EGFR-mutant Asian patients, it has been examined the effectiveness of continuing erlotinib therapy (used as a first-line treatment) after the progression. The study included a total of 207 patients; 81 of the 150 progressed patients continued to receive erlotinib, while the rest of the patients discontinued. The result showed better PFS with the continuation of erlotinib (9.3 months vs. 7.2 months) [19]. Although further randomized studies are required to better clarify this approach, it can be considered, especially for asymptomatic cases with slow progression [5].

Combining the EGFR-TKI with Other Agents

In this combined approach, EGFR-TKIs are combined with chemotherapy or other targeted agents. Among these, the combined-chemotherapy approach has been recommended based on the potential heterogeneity in EGFR-TKI resistance. As part of the combined-chemotherapy approach, patients continue to receive EGFR-TKIs to inhibit sensitive clones, and they are also administered chemotherapy to eliminate EGFR-TKI-resistant clones. The IMPRESS study (phase III) conducted in this article randomized patients progressed under the gefitinib treatment into cisplatin/pemetrexed or cisplatin/pemetrexed/gefitinib. Chemotherapy combined with gefitinib did not significantly contribute to survival (PFS: 5.4 months for both arms), concluding that platinum-based combined chemotherapy was the standard approach [20].

Combining the EGFR-TKI, which is administered as a first-line treatment, with other targeted agents after progression seems to be attractive as it has potentially advantages of the blocking of progression by two different ways. Cetuximab has been a prominent agent in this manner. After a preclinical study [21] showed that an afatinib/cetuximab combination overcame erlotinib resistance, a phase Ib study was conducted on this combination. This study, which included 126 cases that progressed under erlotinib/gefitinib, obtained a response rate and PFS of 29% and 4.7 months, respectively. Analysis

Table 3. Clinical studies conducted with third-generation TKIs

			ORR (%)			DCR (%)			PFS (months)		
Study	**TKI**	**Phase**	**Total**	**T790M-**	**T790M+**	**Total**	**T790M-**	**T790M+**	**Total**	**T790M-**	**T790M+**
AURA [28]	Osimertinib	I/II	51	21	61	84	61	95	8.2	2.8	9.6
AURA2 [29]	Osimertinib	II	64	NA	64	90	NA	NA	NA	NA	NA
Austrian Study [31]	Osimertinib	II	93	NA	93	100	NA	100	NA	NA	NA
AURA3 [32]	Osimertinib	III			71 vs. 31						10.1 vs. 4.4
TIGER-X [34]	Rociletinib	I/II	NA	29	59	NA	59	93	NA	5.6	13.1

TKI: tyrosine kinase inhibitor; ORR: objective response rate; DCR: disease control rate; PFS: progression-free survival; NA: not available

of patients as T790M+ or T790M- revealed similar results between the two groups [22]. On the other hand, another phase I/II study with a similar patient group reported no response with the erlotinib/cetuximab combination after erlotinib resistance [23]. Therefore, further studies are required to expand the cetuximab combination to all agents and to the whole patient group.

Second-Generation EGFR-TKIs

With resistance developed against first-generation EGFR-TKIs, second/third-generation TKIs have attracted all the attention. Afatinib, dacomitinib, and neratinib are the main second-generation TKIs, and they are able to bind irreversibly to EGFR with a high affinity. In addition, they block other members of the HER family, namely HER-2, HER-3, and HER-4. Relevant clinical studies have been conducted after preclinical studies demonstrated that those agents reversed first/second-generation EGFR-TKI resistance [24]. Regarding clinical studies conducted with afatinib, there is the LUX-Lung-1 study, which compared afatinib with placebo in patients progressed under EGFR-TKI treatment. Despite better PFS (3.3 vs. 1.1 months), the overall survival presented no significant difference (10.8 vs. 12.0 months) [25]. Although the LUX-Lung-1 and LUX-Lung-6 studies that examined the effectiveness of afatinib as a first-line treatment demonstrated its usefulness, the second-line treatment results fell short of expectations [26]. Likewise, studies on dacomitinib and neratinib could not present satisfactory results. This is considered to be associated with the high gastrointestinal and skin toxicities of this group of drugs, caused by their narrow therapeutic index. For instance, it has been reported that afatinib equally affected WT-EGFR and EGFR T790M+, and thus, the side effects limited T790M+ inhibition at therapeutic doses [27].

Third-Generation EGFR-TKIs

Primary, third-generation EGFR-TKIs include osimertinib (AZD9291), rociletinib (CD-1686), HM61713, EGF816, and ASP8273, which are mutant-selective, sparing the wild-type EGFR and targeting T790M in particular. Their most important characteristic is a quite low affinity to the wild-type EGFR. This eliminates the narrow therapeutic index problem related to toxicity, which is observed in first- and second-generation EGFR-TKIs.

Osimertinib (Tagrisso, AZD9291) is an irreversible EGFR-TKI that targets the cysteine-797 residue in the EGFR's ATP-binding site and binds to this site with a covalent bond. Following preclinical studies demonstrating its high effectiveness on T790M mutation, in particular, clinical studies have been conducted with osimertinib. The first was a phase I study (AURA) that reported an overall response rate (ORR) of 51% and a disease control rate (DCR) of 84% with osimertinib in progressed patients with a history of EGFR-TKI treatment. With respect to T790M status, ORR, DCR, and PFS were found to be 61%, 95%, and 9.6 months in T790M+ patients and 21%, 61%, and 2.8 months in T790M- patients, respectively. Diarrhea (47% for all grades), rash (40%), and nausea (22%) were the most common side effects; however, dosage reduction due to side effects and treatment discontinuation rates were reported to be low (7% and 6%, respectively) [28]. AURA-2 is a phase II study that investigated the effectiveness of osimertinib on T790M+ patients progressed under EGFR-TKI treatment. The total response rate and DCR were 64% and 90%, respectively, PFS did not reach the median value, and side effects were reported as diarrhea (34% for all grades), rash (40%), and interstitial lung disease (1.9%), which were similar to those of previous studies [29]. Osimertinib has also been reported to be highly effective in central nervous system (CNS) metastases. A combined analysis of AURA and AURA-2 studies evaluated 39 metastatic patients and found the ORR as 56% and 64% in metastatic and non-metastatic patients, respectively [30]. Following these developments, osimertinib received an accelerated approval by the Food and Drug Administration (FDA). As part of another study based on real-life data, which was presented at the annual American Society of Clinical Oncology meeting in 2016, 30 T790M+ patients progressed after the first/second-line EGFR-TKI received osimertinib with 23% complete response, 70% partial response, and 7% stable disease response rates [31]. In the AURA-3 trial, osimertinib was compared with platinum + pemetrexed as second-line therapy in 410 patients with T790M+ who had progressed on EGFR-TKI treatment. Osimertinib showed superiority to chemotherapy in terms of response rate (71% vs. 31%) and PFS (10.1 months vs. 4.4 months) in whole group. This superiority has also been observed in patients with brain metastasis [32]. There are ongoing studies on osimertinib in the article of different lines, including adjuvant therapy (Table 3).

Rociletinib (CO-1686) is another third-generation EGFR-TKI. Rociletinib is EGFR-mutant-selective; it targets commonly monitored EGFR mutations, particularly T790M, and spares the WT-EGFR at the same time [33]. As part of a phase I/II study (TIGER-X), researchers carried out a dosage determination trial for 130 EGFR-mutant NSCLC patients who acquired resistance after EGFR-TKI treatment. This study employed a

re-biopsy to document secondary resistance. The T790M+ patient group presented an ORR and PFS of 59% and 13.1 months, which were reported as 29% and 5.6 months, respectively, for the T790M- patient group. Rociletinib also exhibits a reasonable toxicity profile with hyperglycemia (47% for all grades), nausea (35%), and fatigue (24%) as the most prevalent side effects (Table 3) [34]. The hyperglycemic side effect is suggested to be primarily associated with the metabolite M502, which causes hyperglycemia by blocking the insulin growth factor type-1 receptor and insulin receptor [33]. Rociletinib has also been demonstrated to be effective on CNS metastases. One hundred and seventy (42%) of 401 patients who received rociletinib were CNS-metastatic, and their response rate was reported as 41% [35]. After such developments, rociletinib was granted a "breakthrough therapy designation" by the FDA. There is an ongoing phase III study (TIGER-3), as part of which rociletinib is compared with a chemotherapy regimen preferred by the researcher for patients progressed after EGFR-TKI treatment or chemotherapy [36].

Other third-generation EGFR-TKIs, namely HM61713, EGF816, and ASP8273, are also irreversible TKIs; they are EGFR-mutant-selective, targeting commonly monitored EGFR mutations and T790M, in particular, and sparing the WT-EGFR. These agents are reported to show a 60-fold higher affinity to the mutant EGFR than does the WT-EGFR. Phase I studies conducted on these agents have reported similar response rates, survival rates, and toxicity characteristics to those observed with osimertinib and rociletinib [5,7].

Positive results obtained with all these agents both are promising for the resistant disease and show the importance of revealing resistance mechanisms by a re-biopsy in the case of progression and planning of treatment accordingly. Nevertheless, a re-biopsy sometimes becomes impossible due to the location of the primary tumor or refusal by the patient. In such cases, molecular analyses may be performed based on the circulating tumor cell DNA (ctDNA) through a liquid biopsy [37]. As the patients may potentially develop resistance to EGFR-TKIs after a while, it is useful to carry out repetitive tissue/liquid biopsies when progression takes place after each treatment.

Approaches to Other Pathways

C-MET activation is a significant cause of secondary resistance to EGFR-TKI treatment. This resistance mechanism, which frequently manifests as gene amplification, represents approximately 20% of all cases. As part of a phase II study conducted with capmatinib (INC280), a potent and selective c-MET inhibitor, c-MET-positive patients who progressed after EGFR-TKI treatment were administered capmatinib + gefitinib with 18% partial response rate, 62% stable disease rate, and 80% DCR [38]. There is an ongoing phase I/II study comparing capmatinib with chemotherapy [38].

Immunotherapy is an alternative treatment option when the patient develops resistance to first/second-generation EGFR-TKIs. Regarding immunotherapy, which has recently drawn a great deal of attention, a series of studies have been conducted with various immune checkpoint inhibitors in the advanced stage of the disease, and some of those agents have been included in treatment guides upon the FDA's approval [39,40]. Moreover, preclinical studies have demonstrated that the mutant EGFR directs the programmed death-ligand 1 expression, and the blocked PD-1 receptor increased survival in EGFR-mutant rats [7]. This is considered likely to take place through the stimulation of tumor cell death by EGFR-TKI treatment, followed by the stimulation of the immune system by a release of antigens [41]. Based on these findings, a limited number of patients were administered a combination of nivolumab (anti-PD-1 monoclonal antibody) and erlotinib, and the ORR was reported as 19% (three out of four patients with a response had progressed under erlotinib treatment) [42].

There are other approaches combining third-generation EGFR-TKIs with immune checkpoint inhibitors. Among them, a phase I study combining osimertinib and durvalumab reported a 57% partial response rate in a group of T790M+ patients [43]. Although the combination of these two groups of drugs offers theoretical and clinical advantages, it also brings about the risk of increased toxicity. Therefore, a clarification of the optimal dosage, scheme, and order of administration will reduce concerns in this regard.

In conclusion, first/second-generation EGFR-TKIs have long become the standard approach to the treatment of advanced-stage NSCLC patients with a sensitive EGFR mutation. Nevertheless, as secondary resistance-and hence, progression-becomes inevitable after a while, the principles of approach should be better established. Today, third-generation EGFR-TKIs are the most frequently employed approach in the transition to chemotherapy, and they are very promising thanks to their highly specific activity and low toxicity profiles. Besides, they also constitute alternative options in the transition to immunotherapy and in combination with other agents. Further clarification of the molecular patterns of secondary resistance will enable more specific treatments in the future.

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ORIGINAL ARTICLE

Clinical and Serological Features of Eosinophilic and Vasculitic Phases of Eosinophilic Granulomatosis with Poliangiitis: a Case Series of 15 Patients

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Abstract

OBJECTIVES: Eosinophilic granulomatosis with poliangiitis (EGPA) which was previously called Churg-Strauss Syndrome, is classified into eosinophilic and vasculitic phases. To characterize the eosinophilic and vasculitic phases of the disease in terms of clinical findings, serology, and treatment.

MATERIALS AND METHODS: We included 15 EGPA patients in the study. The clinical, serological, and therapeutic characteristics and the treatment responses of the patients were recorded.

RESULTS: Thirteen patients were classified as being in the eosinophilic phase and two were classified as being in the vasculitic phase of EGPA. Initial symptoms were worsening asthma in all patients (n=15; 100%). All patients had rhinosinusitis, and 66.6% had hypersensitivity to nonsteroidal anti-inflammatory drugs. The two patients in the vasculitic phase did not have nasal polyposis. Pulmonary and nervous system involvement were the most common symptoms. The erythrocyte sedimentation rates (ESRs) of the two patients in the vasculitic phase were 65 mm/h and 55 mm/h, while ESR was normal in eosinophilic-phase patients. Antineutrophil cytoplasmic antibodies (ANCA) was detected in one patient (6.6%) who was in the vasculitic phase (Case 15). The disease was under control with higher doses of methylprednisolone in the vasculitic phase (Case 14: 12 mg/day, Case 15: 10 mg/day) than in the eosinophilic phase. Relapse was detected in the two patients in the vasculitic phase. Oral corticosteroid was not discontinued in any case, and no mortality was reported.

CONCLUSION: Patients with eosinophilic phase or vasculitic phase EGPA had similar clinical onset. However, higher ESR, ANCA positivity, and extrapulmonary organ involvement were only found in patients in the vasculitic phase. Corticosteroid responsiveness was very good in all patients in the eosinophilic phase, and the disease could be controlled with a very low maintenance dose of a corticosteroid.

KEYWORDS: Asthma, Churg-Strauss syndrome, eosinophilic granulomatosis with poliangiitis, eosinophilic phase, vasculitic phase

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INTRODUCTION

Eosinophilic granulomatosis with poliangiitis (EGPA), which was previously called Churg-Strauss syndrome, is a necrotizing systemic vasculitis of small to medium-sized vessels [1,2]. The criteria used for classification of vasculitis were established by the American College of Rheumatology (ACR). These criteria can only be used to define vasculitis type and cannot be used for diagnosis. The criteria consist of the following six items: asthma, eosinophilia (>10%), neuropathy, migratory pulmonary infiltrates, paranasal sinus abnormalities, and biopsy-proven extravascular eosinophils. Diagnostic yield for EGPA is reported with a sensitivity of 85% and a specificity of 99.7% when at least four of these criteria are met [3,4]. Although EGPA belongs to the spectrum of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, ANCA positivity is reported to be approximately 40-60%. The necrotizing vasculitis is missed in many pathological studies, but non-destructive eosinophilic infiltration can be detected in the vessel walls of most of the patients [5].

The manifestation of the disease varies from mild disease- including asthma, nasal polyps, and cutaneous lesions- to severe gastrointestinal (GI) or heart involvement and disabling multiplex mononeuropathies [6,7], which can be life threatening. EGPA is usually described as going through the following three phases: 1) *Prodromal phase*: Allergic rhinitis, recurrent sinusitis, and nasal polyposis, 2) *Eosinophilic phase*: eosinophilia in the peripheral blood and tissues without proven vasculitis, and 3) *Vasculitic phase:* constitutional symptoms such as fever, weight loss, fatigue, and vasculitis of small to medium-sized vessels [6,7].

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In this study, we characterized patients with EGPA. The baseline characteristics, clinical manifestations, phases at time of diagnosis, and treatment responses of the disease were analyzed. The clinical and serological features of both the eosinophilic and vasculitic phases of the disease were also evaluated.

MATERIALS AND METHODS

The Ethics Committee of Erciyes University approved the study protocol, and all subjects provided written informed consent. Fifteen patients with EGPA who were admitted to the Chest Diseases Department of Erciyes University Hospital between May 2012 and May 2014 were included in this study. The following clinical, serological, and pathological data obtained from medical records were reviewed and evaluated.

Patient characteristics: age, sex, smoking history, age at the diagnosis, atopy, nasal polyposis, allergic rhinitis and/or rhinosinusitis, asthma, non-steroid anti-inflammatory drug (NSAID) hypersensitivity, and NSAID-exacerbated respiratory disease (NERD).

Laboratory and functional tests: blood eosinophilia, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), total immunoglobulin E (IgE), ANCA, troponin, urinalysis, liver and renal function tests, and pulmonary function tests, including forced expiratory volume in first second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC.

Imaging tests: high-resolution computerized tomography of thorax (HRCT), paranasal sinus computerized tomography (PNSCT), echocardiography (ECHO), electromyography (EMG), and cranial magnetic resonance imaging (MRI).

Treatment: Systemic corticosteroids and immunosuppressants.

Prognosis data: Relapse rates and survival.

The eosinophilic phase of EGPA was diagnosed if four or more of the ACR criteria were met after excluding other causes of eosinophilic infiltration. The vasculitic phase was diagnosed when four or more of the ACR criteria were met along with biopsy-proven vasculitis.

The following systems were examined for organ involvement: The peripheral nervous system (PNS) and the central nervous system (CNS), the kidneys, the heart, the GI tract, the lungs, and the skin. EMG-confirmed mononeuropathy or polyneuropathy was considered as peripheral neurological involvement. Cardiac involvement was diagnosed by ECHO and increased troponin without other risk factors. Renal involvement was diagnosed with increased serum creatinine, proteinuria, or abnormal urinary sediment that could not be attributed to other diseases. Lung involvement was diagnosed by the presence of centrilobular nodules, bilateral ground glass opacities, and thickened bronchial wall on HRCT. Involvement of GI the tract was diagnosed by unexplained abdominal pain, nausea, vomiting, diarrhea, and hemorrhage during a vasculitic flare after excluding any other possible underlying etiology and was proven by endoscopic biopsy.

The occurrence or reappearance of EGPA features other than asthma was considered as relapse. Remission was considered when the patient was symptom-free for at least one year [8]. Asthma or sinusitis exacerbations, with or without eosinophilia, were considered as alterations in disease activity, also called grumbling disease, but not as relapse.

Statistical Analysis

Statistical analyses were performed in Statistical Package for the Social Sciences version 15.0 (SSPS Inc.; Chicago, IL, USA). A One-Sample Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables for normality, and data were presented as mean±standard deviation (SD) or median and quartiles where appropriate. Categorical variables were expressed as frequencies and percentages.

RESULTS

Out of 15 cases, 11 were female with a mean age of 44.1±9.8 years. The youngest age at diagnosis was 22 years. Dyspnea was the presenting symptom of all patients, and they all had asthma and rhinosinusitis at the time of diagnosis of EGPA (Table 1). Ten (66.6%) had comor-

Table 1. Characteristics of patients with EGPA at the time of diagnosis

Female, n (%)	11 (73.3)
Age at the time of diagnosis, mean±SD, years	42±9.8
Follow-up duration, mean±SD, (range), years	1.7±0.5 (0.5-2)
Smoking, n (%)	
Current smokers	1 (6.6)
Ex-smokers	2 (13.3)
Non-smokers	12 (80)
Housewife, n (%)	10 (66.6)
Presence of atopy, n (%)	3 (20)
Pollens, n (%)	3 (20)
House dust mites, n (%)	3 (20)
Molds, n (%)	1 (6.6)
Underlying disorders, n (%)	
Asthma	15 (100)
Rhinosinusitis	15 (100)
Nasal polyps	10 (66.6)
NSAID hypersensitivity	10 (66.6)
Asthma duration before diagnosis [median, (range)], years	10 (1-30)
Nasal polyposis duration before diagnosis [median, (range)], years	10 (3-20)
Hospitalization due to asthma in preceding years mean±SD	1.1±0.8
Admission to emergency room due to asthma in preceding years mean±SD	6±2.7

SD: standard deviation; NSAID: non-steroid anti-inflammatory drug

bid NSAID hypersensitivity. All of the patients had severe asthma and were prescribed step 4 or step 5 medications according to the GINA guideline [9]. They were followed for 1.7±0.5 years (range: 0.5-2 years). All had peripheral blood eosinophilia (21.2%±11.1%) (Table 2). ANCA was detected in one patient (6.6%) who was in the vasculitic phase (Case 15).

Upper airway pathologies, which were present in all cases, were documented on PNSCT and rhinoscopy. Ten patients (66.6%) had nasal polyposis. The two patients in the vasculitic phase (13%) had PNS damage that was documented with EMG (Table 3). Only two patients were biopsied, which included the GI tract (Table 4), and vasculitis was confirmed in the two GI tract biopsies. Two cases were considered to be in the vasculitic phase, and there were no signs of extrapulmonary involvement in the other 13 cases, which were considered as being in the eosinophilic phase. The HRCT lesions of all patients (both eosinophilic phase and vasculitic phase) were compatible with EGPA (Figure 1 and 2), and all patients met at least 4 criteria of the ACR.

Table 2. Laboratory, functional, and radiological data at the time of diagnosis of patients with EGPA

Eosinophil mean±SD, %	21.2±11.1
Total IgE, median (range), IU/mL	194 (45-2,974)
ESR, mean±SD, mm/h	18.1±18.3
CRP, mean±SD, mg/L	6.1±6
FEV_1, mean±SD, %	61.4±10.5
Thorax (HRCT), n (%)	
Ground-glass opacities	15 (100)
Centrilobular nodules	4 (26.6)
Bronchial wall thickening	3 (20)
Alveolar consolidation	2 (13.3)

EGPA: eosinophilic granulomatosis with poliangiitis; IgE: Immunoglobulin E; SD: standard deviation; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; FEV_1: forced expiratory volume in first second; HRCT: high-resolution computerized tomography of thorax

Response to initial glucocorticoid treatment was good in all patients. Only one patient was given additional immunosuppressive treatment with methotrexate (case 15). All were on oral corticosteroid treatment, 6±2.4 mg/day (range: 2-12 mg/day) methyl prednisolone. The disease was kept under control with higher methyl prednisolone doses in patients in the vasculitic phase (Case 14: 12 mg/day, Case 15: 10 mg/day) than those in the eosinophilic phase. None of the patients could discontinue oral corticosteroid treatment.

The majority of our patients (86.6%) experienced remission on treatment. Two patients (13.3%) experienced a disease relapse. Both of these patients were in the vasculitic phase, and the cause of relapse was lung involvement in both cases. Grumbling disease was experienced by all cases, and no mortality occurred on follow-up.

Table 3. Diagnostic criteria of patients with EGPA (n=15)

Patient no.	ACR Criteria number*	Asthma	Nasal polyposis	Analgesic hypersensitivity	Paranasal sinus abnormality (PNSCT)	Pulmonary infiltrates on thorax HRCT	Polyneuropathy (history and EMG), CNS involvement (Cranial MRI)	Biopsy containing a blood vessel with extravascular eosinophils
1	4	+	+	-	+	+		
2	4	+	+	+	+	+	-	
3	4	+	+	+	+	+	-	
4	4	+	+	+	+	+	-	
5	4	+	+	+	+	+	-	
6	4	+	+	+	+	+	-	
7	4	+	+	-	+	+	-	
8	4	+	-	-	+	+	-	
9	4	+	-	+	+	+	-	
10	4	+	+	+	+	+	-	
11	4	+	+	-	+	+	-	
12	4	+	+	+	+	+	-	
13	4	+	-	-	+	+	-	
14	6	+	-	+	+	+	+	+ (GI tract)
15	6	+	-	+	+	+	+	+ (GI tract)

*the number of ACR criteria present. EGPA: eosinophilic granulomatosis with poliangiitis; ACR: American College of Rheumatology; PNSCT: paranasal sinus computerized tomography; HRCT: high-resolution computerized tomography of thorax; EMG: electromyography; CNS: central nervous system; MRI: magnetic resonance imaging; GI: gastrointestinal

Table 4. Damaged organs and laboratory and functional data in patients with EGPA

	Damaged organs								Eosinophil	ESR	ANCA
Patient No.	CNS	PNS	Heart	Lung	GI	Kidney	Skin	UA	%	mm/h	
1	-	-	-	+	-	-	-	+	18	18	-
2	-	-	-	+	-	-	-	+	14	2	-
3	-	-	-	+	-	-	-	+	12	2	-
4	-	-	-	+	-	-	-	+	22	10	-
5	-	-	-	+	-	-	-	+	23	19	-
6	-	-	-	+	-	-	-	+	58	19	-
7	-	-	-	+	-	-	-	+	16	10	-
8	-	-	-	+	-	-	-	+	18	8	-
9	-	-	-	+	-	-	-	+	29	10	-
10	-	-	-	+	-	-	-	+	14	20	-
11	-	-	-	+	-	-	-	+	20	2	-
12	-	-	-	+	-	-	-	+	23	20	-
13	-	-	-	+	-	-	-	+	14	10	-
14	-	+	-	+	+	-	-	+	20	55	-
15	-	+	-	+	+	-	-	+	18	65	+

CNS: central nervous system; PNS: peripheral nervous system; GI: gastrointestinal;
UA: upper airway; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ANCA: antineutrophil cytoplasmic antibody

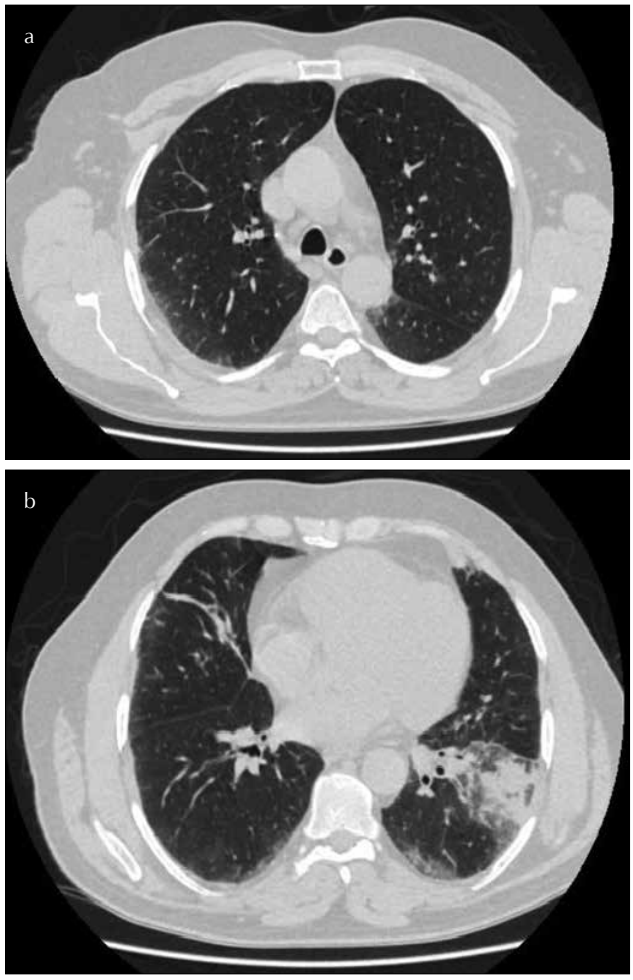

Figure 1. Centrilobular nodules mostly within the ground-glass opacity. Airspace consolidation, subpleural, and surrounded by the ground-glass opacity

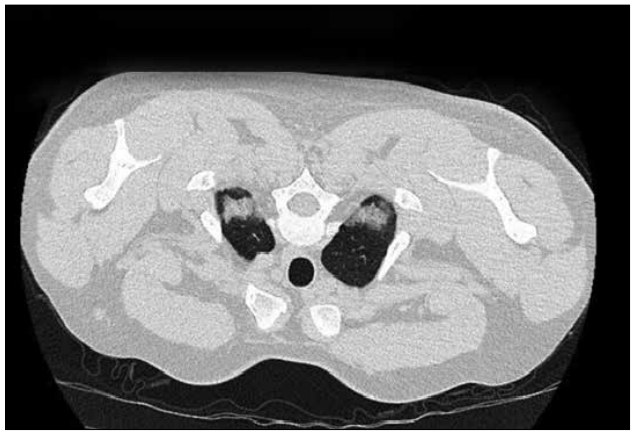

Figure 2. Bilateral ground-glass opacity in the upper lobes

DISCUSSION

Our case series had some important characteristics of EGPA phases. Although age, gender distribution, and prodromic EGPA phase were similar to previous studies, the organ/system involvements were different. The majority of patients were in the EGPA eosinophilic phase, and increased ESR, ANCA positivity, and extrapulmonary organ involvement were only found in the patients in the vasculitic phase. Corticosteroid responsiveness was very good in all patients in the eosinophilic phase, and the disease could be controlled with a very low maintenance dose of a corticosteroid.

Nasal polyposis and recurrent sinusitis characterize the prodromic EGPA phase [10]. Nasal polyps affect approximately half of the patients and can recur after surgery in patients not receiving immunosuppressive therapy [11]. In our study, the upper airways were affected in all patients, and two thirds of the patients had nasal polyposis. However, the two patients in the vasculitic phase did not have nasal polyposis.

These rates were similar to those of other studies [10-12]. The rate of NSAID hypersensitivity was similar (66%) to our previous study [12]. NSAID hypersensitivity is characterized by exacerbation of bronchoconstriction and other symptoms of asthma and/or upper airway symptoms (nasal congestion, rhinorrhea, and itching) after use of acetylsalicylic acid and/or other NSAIDs. In particular, hypersensitivity to cyclooxygenase-1 enzyme inhibitors is frequent among the EGPA cases with severe asthma [13]. This condition is also called aspirin-exacerbated respiratory disease or NSAID-exacerbated respiratory disease. Recurrent nasal polyps and increased peripheral eosinophilia are among the common characteristics of EGPA [14].

Commonly involved organs are the upper airway tract, lung, skin, heart, GI tract, and nervous system. The kidney is not a commonly affected organ in EGPA, but it might be involved in some patients, especially those with ANCA positivity [15]. The involved organs in our study had partial similarity with what has been seen in previous larger studies [6,8,16-18]. The lung was the most commonly involved organ in our series, and all of the patients in the eosinophilic phase only had pulmonary involvement. The clinical manifestations of patients referred to our department, which included asthma, eosinophilia, and pulmonary infiltrates, were most likely caused by lung involvement. Although PNS involvement was the second most commonly involved system in our series, its frequency was lower than in previous studies [6,8,16-18]. PNS involvement was only detected in patients in the vasculitic phase. GI system involvement was also only detected in patients in the vasculitic phase. GI tract involvement was also lower in our study with a frequency of 13.3% [6,8,16-18]. None of the patients had skin, heart, CNS, or renal system involvement.

The majority of the patients in our study were considered as being in the EGPA eosinophilic phase. EGPA and other small and medium-sized vessel vasculitides have been defined as clinicopathological entities to underline the fact that they require a combination of clinical and histopathological findings in order to be diagnosed with confidence [1-4,19]. The diagnosis of the eosinophilic phase of EGPA is rapid and convenient because pathological evidence is not mandatory in the ACR criteria. Thus, delayed diagnosis and the irreversible morbidity rate can decrease. However, using the criteria for diagnostic purposes might lead to the risk of overdiagnosis of the eosinophilic phase of EGPA in patients with milder eosinophilic diseases and might lead to overtreatment. In differential diagnosis of the EGPA eosinophilic phase, parasitic infections, chronic eosinophilic pneumonias, hypereosinophilic syndrome, NERD, allergic bronchopulmonary aspergillosis, microscopic polyangiitis, granulomatosis with polyangiitis (Wegener's), lymphoreticular malignancies, and collagen vascular diseases should be considered. We considered all possibilities in the differential diagnosis of EGPA eosinophilic phases. Coincidental bacterial or viral pneumonia can occur in conjunction with asthma and eosinophilia, and therefore pneumonia must be excluded for the differential diagnosis of the EGPA eosinophilic phase. In our patients, pneumonia was ruled out by means of the patients' clinical and laboratory findings and corticosteroid response without antibiotics.

Thirteen patients in the eosinophilic phase met 4 criteria, and all of them had the prodromic phase of EGPA. In the present study, eosinophilic and vasculitic phase differentiation was not shown with transbronchial biopsy in patients who were considered to be in the eosinophilic phase of EGPA. Bronchoscopy could not be performed in these patients because they had severe asthma attacks at the time of diagnosis. Because of small-vessel vasculitis, the patients did not exhibit typical characteristics of vasculitis, which is considered by the combination of constitutional symptoms and paradoxical improvement of asthma. ESR is expected to be higher, especially during the phase of active vasculitis. Our patients who were considered to be in the eosinophilic phase had none of the above. ESR was normal in patients in the eosinophilic phase of the disease, while ESR was greater than 50 mm/h in patients in the vasculitic phase.

Anti-neutrophil cytoplasmic antibody positivity is an important laboratory finding of EGPA, and ANCA positivity, renal disease, peripheral neuropathy, and pulmonary hemorrhage are frequent among EGPA patients. Endomyocardial involvement and lung infiltrates are more common in the ANCA-negative subset [20]. ANCA, with an immunofluorescence pattern usually consisting of P-ANCA and anti-MPO specificity, is present in up to 40% of EGPA patients, but only a minority of patients have cytoplasmic ANCA with antibodies to proteinase 3 [21-23]. In our study, only one of the 15 patients (6.6%) was positive for ANCA, and this patient was in the vasculitic phase. The low ANCA profile in our study might be associated with low renal disease rate, as well as GI, neural system, and pulmonary involvement without hemorrhage.

Glucocorticoids and immunosuppressive treatments form the cornerstone of therapy for improved prognosis and survival rates of EGPA patients if they are given early [22,23]. The Five-Factor Score (FFS) is usually used to determine prognosis in EGPA, and patients with FFS ≥1 have a worse prognosis and higher mortality [17,24]. FFS consist of the following items: age >65 years, heart involvement, renal insufficiency, GI involvement, and ENT manifestations, which are associated with better outcomes, and ENT involvement absence is associated with a good prognosis [25]. In our study, only the two patients in the vasculitic phases had poor prognostic factors. In the patients in the vasculitic phase, it was possible to control the disease with higher doses of corticosteroids compared to patients in the eosinophilic phase of EGPA. Although we could not discontinue corticosteroid treatment, the disease activity was under control with low doses in the eosinophilic phase of EGPA.

In conclusion, patients in the eosinophilic phase or vasculitic phase of EGPA had similar clinical onsets. However, higher ESR, ANCA positivity, and extrapulmonary organ involvement were only found in patients in the vasculitic phase. Corticosteroid responsiveness was very good in all patients in the eosinophilic phase, and the disease could be controlled with a very low maintenance dose of a corticosteroid.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.Y.; Design - İ.Y., N.T.; Supervision - İ.Y., N.T., İ.G.; Data Collection and/or Processing - İ.Y., Z.Ö.Ş.; Analysis and/or Interpretation - İ.Y., N.T., İ.G., Z.Ö.Ş., F.S.O.; Literature Search - İ.Y., N.T., İ.G., Z.Ö.Ş., F.S.O.; Writing Manuscript - İ.Y., N.T., İ.G., Z.Ö.Ş., F.S.O.; Critical Review - İ.Y., N.T., İ.G.

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ORIGINAL ARTICLE

Does the Incidence and Mortality of Pulmonary Thromboembolism Change Over the Years?

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Abstract

OBJECTIVES: In the last 20 years, with the use of computed tomography (CT) angiography, the number of patients diagnosed with pulmonary thromboembolism (PTE) has increased. At the same time, data show that pulmonary embolism mortality has also reduced in this duration.

MATERIAL AND METHODS: In this study, we analyzed records of patients with PTE (using ICD's) in the hospital automation system from 2001 to 2013. Data regarding age, sex, date of diagnosis, diagnosis of cancer, hemodynamic status, initial and maintenance treatment, hospital length of stay, and hospital mortality were recorded. Primary endpoints of the study were hospital length of stay and all-cause hospital mortality.

RESULTS: The total number of patients included in the study was 1185. The median age was 61 years in 2001 and 71 years in 2013. The number of patients who were diagnosed using CT increased from 10% to 92.8%. Between 2001 and 2013, the number of patients diagnosed with PTE increased, and of all patients with PTE, 13.7% was diagnosed in 2009. The hospital length of stay of 13 days declined to 9 days. The use of a vena cava filter in 2007 was 1.1% and that in 2013 was 4.6%. Mortality rate was 15%, however hospital mortality did not significantly differ over the years but varied between 9.4% and 18.8%. Increased use of thrombolytics in patients with massive PTE has been observed over the years. Massive PTE ratio in 2006 was 8.5% and thrombolytic use was 5.8%, however in 2013, these ratios were 2.6%, 6% respectively (p=0.017).

CONCLUSION: Finally, despite the increased number of patients diagnosed with PTE over the years, the mortality rate was not observed to have changed from 2001 to 2013.

KEYWORDS: Pulmonary thromboembolism, heparin, thrombolytic, mortality, incidence

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INTRODUCTION

Pulmonary thromboembolism (PTE) is an important public health concern that causes mortality and morbidity. Its non-specific symptoms and findings lead to difficulties in confirming its diagnosis. However, with the use of computed tomography (CT) angiography in recent years, an important step has been taken in the diagnosis of PTE. Moreover, improvements, such as the development of new anticoagulants and mechanical interventions, have occurred in the treatment of PTE. In parallel with all these improvements, data on the incidence and outcomes of the disease seems to be restricted.

In a study conducted in USA the incidence of PTE was reported to increase from 23/100,000 to 65/100,000 [1]. On the other hand, in a study conducted in Canada, no significant change was observed in the incidence of PTE in the last decade [2]. A study was conducted on 60853 patients in Italy, and an increase was found in the incidence of PTE in the last 10 years [3]. In our study, the data of patients diagnosed with PTE between 2001 and 2013 were obtained from hospital recordings and were analyzed.

MATERIAL AND METHODS

In our study, the records of patients diagnosed with PTE between 2001 and 2013 were obtained from the hospital's automations system (with the International Classification of Diseases ICD I26.0 and I26.9 coding system) and analyzed. The study was performed after approval from the local ethics committee of Karadeniz Technical University (ethics committee number: 2016/55).Because retrospective design of the study, written informed consent was obtained. Other causes of PTE (fat embolism, septic embolism, etc.) were ruled out by examining the epicrises of the patients.

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Data on age, sex, diagnosis dates, diagnostic methods, presence of cancer, hemodynamic states, first-line and maintenance treatments, hospitalization length, and in-hospital mortality were recorded. The primary endpoint was considered to be in-hospital mortality and hospitalization length.

A systolic arterial blood pressure of <90 mmHg at admission was taken into consideration for the diagnosis of massive PTE. However, PTE was defined as massive only in patients requiring a mechanical ventilator during hospitalization and developing hypotension in the follow-up period.

Statistical Analysis

The Kolmogorov-Smirnov test was used for the parametric and non-parametric distribution of data. Data were presented as mean±SD and median±interquartilee range. A p-value of <0.05 was accepted to be significant. Data were recorded on Statistical Package for the Social Sciences (version 13.01, serial number 9069728, SPSS Inc., Chicago) and were analyzed.

RESULTS

A total of 1409 patients were scanned using ICD's (I26.0 and I26.9) between 2001 and 2013. After a complete analysis of patient's records, it was observed that final diagnosis was PTE in 1185 (84.1%). The number of patients diagnosed with PTE gradually increased between 2001 and 2013. The patients diagnosed with PTE in 2009 constituted 13.7% of the total number of patients diagnosed (Figure 1). The median age of all patients was 70 years (range, 57-78 years). While the median age was 61 years (range, 45-75 years) in 2001, it was 71 years (range, 58-80 years) in 2013. The diagnostic method was CT in 92.8% of the patients, perfusion scan in 3.7%, and clinical and Doppler ultrasonography (USG) for investigating the presence of deep venous thrombosis in the remaining 3.5%. While the rate of patients diagnosed by CT was 10% in 2001, it increased to up to 98.4% in 2005 (p<0.001). On the other hand, the rate of diagnosing PTE by scan was 60% in 2001, 56% in 2002, and 18.8% in 2003. During the same years, the rates of diagnosing PTE by clinical and Doppler USG were 30%, 28%, and 3.1%, respectively. General data of the patients are presented in Table 1. While the longest hospitalization length was 13 days (range, 12-20 days) in 2001, it decreased to 7 days (range, 6-13 days) in 2013. (p<0.001) (Figure 2). While the rate of vena cava filter use was 1.1% in 2007, it was 4.6% in 2013.

In our study, the rate of standard heparin (SH) use in the acute phase of PTE in all patients was 45.5% the rate of low molecular weight heparin (LMWH) use was 40.2%, and the rate of thrombolytic use was 5%. While the rate of SH use was 72.1% in 2013, it decreased to 17.1% in 2013 (p<0.001, Table 1).

The general mortality rate was 13% and the in-hospital mortality rate fluctuated between 9.4% and 18.8% over the years from 2001 to 2013. No significant difference was found among the years in terms of the mortality rate

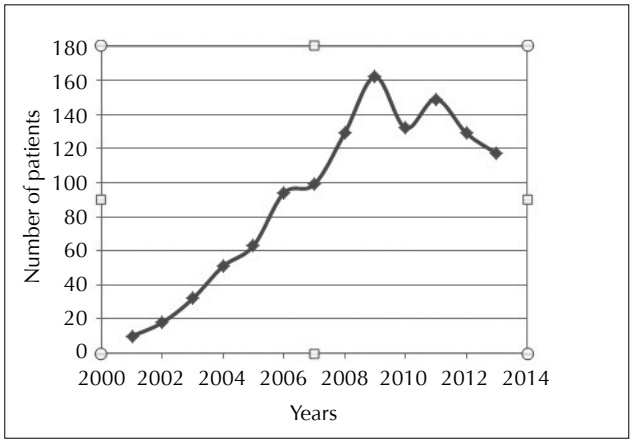

Figure 1. Number of patients over to the years

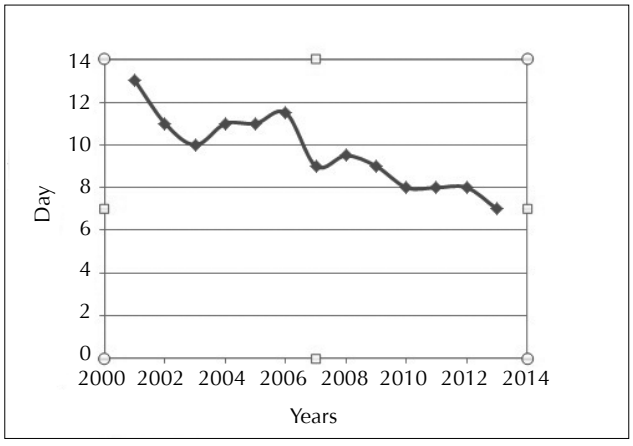

Figure 2. Hospitalization length over the years

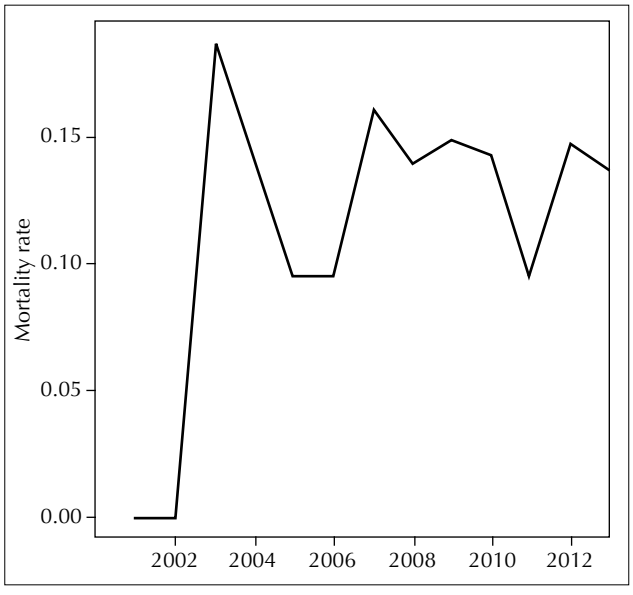

Figure3. Mortality rate over the years

(p<0.05) (Figure 3). While mortality rate was 12.9% in male patients, it was 13.1% in female patients. There was a statistically significant difference between both sexes with regard to the mortality rate.

The rate of thrombolytic use increased in patients with massive PTE over the years. While the rate of massive PTE pa-

Table 1. Change in the rate of pulmonary thromboembolism over the years

Year	Number of patients	Age (median), years	Cancer, %	Males, %	Massive PTE, %	Mortality rate %	Diagnosis by CT %	Thrombolytic use At the beginning %	SH use, %	LMWH use, %	VCF use, %	Hospitalization length, days
2001	10	61	20	20.0	0	0	10					13
2002	18	52	11.1	61.1	0	0	16.7					11
2003	32	63	6.2	50.0	20	18.8	78.1					10
2004	51	66	15.7	41.2	19.6	13.7	98.0					11
2005	63	63	12.7	38.1	19	9.5	98.4					11
2006	94	70	11.7	40.4	8.5	9.6	95.7	5.8	72.1	24.7	-	11.5
2007	99	69	11.2	45.5	12.2	16.2	97.0	9.4	65.6	36	1.1	9
2008	129	70	7	41.1	12.6	14.0	95.3	5	68.3	34.5	5.5	9.5
2009	161	71	10.5	35.8	5	14.8	97.5	2.7	66	41.3	1.4	9
2010	132	71	15.9	16.7	5.3	14.4	96.2	4.6	66.2	56.9	0.9	8
2011	149	69	13	41.6	11.4	9.4	94.6	8.2	50	57.3	0.8	8
2012	129	74	13.4	44.2	7.8	14.7	92.2	5.5	32.8	71.8	3.4	8
2013	117	71	17.6	44.7	2.6	13.7	90.6	6.0	17.1	82.6	4.6	7
Total	1185	70	16.5	38.7	9.2	13	92.8	5	45.5	40.2	1.7	9
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	NS	<0.001	NS	<0.001	0.001	NS	<0.001

VCF: vena cava filter; SH: standard heparin; LMWH: low molecular weight heparin; NS: non-significant

tients was 8.5% in 2006, the rate of thrombolytic use was 5.8%. In 2013, the rate of patients diagnosed with massive PTE was 2.6%, but the rate of thrombolytic use was 6% (p=0.017). Thus, it was observed that thrombolytic use increased in non-massive patients over the years.

DISCUSSION

In this study, it was found that the number of patients diagnosed with PTE gradually increased over time but that the mortality rate did not change. Moreover, an increase in the rate LMWH use was observed both in the acute stage and the maintenance period. While the mean hospitalization length was 13 days in 2001, it was 7 days in 2013. Over the years, the hospitalization length was observed to decrease.

The clinical course of PTE can vary from asymptomatic cases to sudden deaths. Data obtained till date show that the number of patients diagnosed with PTE has increased. Similarly, the number of PTE patients has apparently increased according to our clinical observations. In our study, it was found that the number of patients diagnosed with PTE relatively decreased in 2011. The most important cause for this decrease is that technical capacities and clinical experiences in diagnosing and treating PTE have increased in other hospitals of Eastern Black Sea Region.

The rate of mortality due to PTE has generally decreased over the years. In particular, the detection of clinically insignificant patients can contribute to a decreased mortality rate. In a study conducted in USA, the mortality rate was reported to decrease from 7.1% to 3.2% over 20 years [1]. In another study conducted in Australia, it was revealed that the mortality rate decreased over years but that PTE was still an important cause of mortality and morbidity in females and the elderly population [4]. In our study, the overall mortality rate was around 13%, and no change was observed in the mortality rate over the years. The mortality rate was found to be 13% in our two prospective studies between 2008 and 2009 and between 2012 and 2014 [5,6]. However, while the PTE-related mortality rate was 5.6% in our first study, it was 4.4% in the other one. Based on many factors that can influence the mortality rate, such as accompanying co morbid disorders, the application of clinically more severe patients to our hospital because of the provision of tertiary health care, and not performing autopsy for finding the real cause of death, the mortality rate was not observed to have changed over the years in our current study.

The use of CT for the diagnosis of PTE increased for five times in between 2001 and 2009 [7]. In another study, while no change was found in the incidence of PTE in the years before the use of CT pulmonary angiography, the incidence increased to 81% with the use of CT [8]. Further, in our study, a dramatic increase was observed with the use of CT between 2001 to 2013, compared to the first years. The increased rate of PTE diagnoses may reveal another problem. Complications developing in association with anticoagulant therapy lead to mortality and morbidity. The clinically significant complication of bleeding was reported to have developed at the rate of 12% during anticoagulant use for 3-6 months [9]. An increased number of patients are exposed to radiation; therefore, the effects of radiation damage will be observed in the long term.

In addition, changes in the selection of anticoagulants were also observed over the years. In the present study, the rate of SH use decreased from 72% to 17% (an approximately decrease of 4.5 times). On the contrary, the rate of LMWH use increased from 25% to 82%. In the study by Jimenez et al. on 23858 patients between 2001 and 2013, while the rate

of LMWH use increased from 77% to 84%, that of SH use decreased by around 2.5 times [10].

It has been observed seen that the hospitalization length and high hospital costs has shortened over time due to increased experience of physicians and increased use of LMWHs. In a study conducted in USA, the median hospitalization length was reported to have decreased from 8 days to 4 days [1]. In another study, the median hospitalization length decreased from 13.6 days to 9.3 days within a 13-year period [10]. In our study, the hospitalization length decreased from 13 days to 7 days. In clinical practice, it is seen that accompanying co morbid conditions are one of the most important factors affecting long hospitalization lengths. Another factor that may decrease the hospitalization length is the use of LMWH instead of warfarin because warfarin dosing in maintenance treatment can sometimes take a longer time due to its changing metabolism each other.

This study has some limitations. Firstly, it cannot be suggested that the study included all patients diagnosed with PTE because it was a retrospective, single-center study. Moreover, we do not know the exact number of PTE patients who were coded using other ICDs (dyspnea, respiratory failure, hemoptysis, chest pain, respiratory arrest, etc.) except than I26.0 and I26.9. In addition, we have no data on the treatments that patients received between the 2001 and 2005. Accompanying morbidities of the patients could not be documented. Hence, all-cause mortality was presented. It can be suggested that changes in the morbidity rate can change the mortality rate over the years.

In conclusion, despite the increased number of patients diagnosed with PTE, it was observed that the mortality rate did not change over the years.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Karadeniz Technical University.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.S.Ö.; Design - S.S.Ö.; Supervision - S.S.Ö., M.B.C., Y.B.; Resources - S.S.Ö., M.B.C.; Materials - S.S.Ö, M.B.C.; Data Collection and/or Processing - S.S.Ö., M.B.C., Z.G.D., Y.B., F.Ö., T.Ö.; Analysis and/or Interpretation - S.S.Ö., M.B.C., Y.B.; Literature Search - S.S.Ö., M.B.C.; Writing Manuscript - S.S.Ö., M.B.C., Y.B.; Critical Review - S.S.Ö., M.B.C., Y.B.; Other - S.S.Ö., M.B.C., S.G.D., Y.B., F.Ö., T.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

Organizing Pneumonia as a Histopathological Term

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Abstract

OBJECTIVES: Organizing pneumonia (OP) is an interstitial lung disease characterized by granulation tissue buds in alveoli and alveolar ductus, possibly accompanied by bronchiolar involvement. Histopathologically, OP may signify a primary disease and be observed as a contiguous disease or as a minor component of other diseases. In this study, the clinical significance of histopathological OP lesions and clinical and radiological features of patients with primary OP were examined.

MATERIAL AND METHODS: Between January 2011 and January 2015, of 6,346 lung pathology reports, 138 patients with OP lesions were retrospectively evaluated. According to the final diagnoses, patients were grouped as reactive OP (those with final diagnosis other than OP) and primary OP (those with OP). Patients with primary OP were classified according to etiology as cryptogenic and secondary OP. Radiological evaluation was conducted within a categorization of "typical," "focal," and "infiltrative."

RESULTS: Of 138 patients, 25% were males and the mean age was 54±14 years. Pathologically, 61% of patients had reactive OP and 39% had primary OP. All reactive OP lesions were reported using surgical specimens, and the most frequent primary diagnoses were malignancy (65%), infection (15%), interstitial lung diseases other than OP (7%), and bronchiectasis (5%). Other diagnoses included bullae, foreign body, hamartoma, bronchogenic cyst, and bronchopleural fistula. Of all the primary OP patients, 48 had cryptogenic OP and six had secondary OP. Radiological involvement was consistent with typical OP in 30%, focal OP in 63%, and infiltrative OP in 7% of the patients. All focal OP lesions were defined using surgical resections. Positron emission computed tomography (PET-CT) was recorded in 28 patients. In 11 patients, lymphadenomegaly was comorbid. The mean widest diameter of focal opacity was 2.7±1.2 (1.2-4.9) cm, and the mean the maximum standardized uptake value (SUVmax was 6.1±3.9 (1.7-16.7).

CONCLUSION: OP lesions generally present as a minor component of other diseases. In patients with OP, cryptogenic OP and radiological focal OP is more frequently observed. Most focal OP lesions are detected using surgical resections because of malignant prediagnosis owing to elevated SUVmax.

KEYWORDS: Interstitial lung disease, malignancy, Masson bodies, organizing pneumonia

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INTRODUCTION

Organizing pneumonia (OP) is an interstitial lung disease, and OP patients present with characteristic clinical, radiological, and histological findings. Histopathologically, there are buds of granulation tissue, which are called Masson bodies and consist of exudative materials including connective tissue components, fibrin, and fibroblasts, in the alveolar ducts and alveoli. Bronchiolar involvement may be present [1,2].

The clinical significance of OP as a histologic finding can vary. It can be found around granulomas or cancer tissues or it can develop as a minor component of diffuse lung diseases such as hypersensitivity pneumonitis and eosinophilic pneumonia. When the OP pattern is detected as a diffuse and major finding, it expresses the disease [3,4]. OP has been investigated in terms of its cryptogenic and secondary forms and its radiological features, but no defnite conclusions can be drawn from these studies [5-7].

In this study, we investigated the Clinical signification of histological OP lesions and the clinical and radiological features of primary OP patients.

The present study was presented as oral presentation in the 19th Turkish Thoracic Society Annual Congress, Antalya, Turkey.
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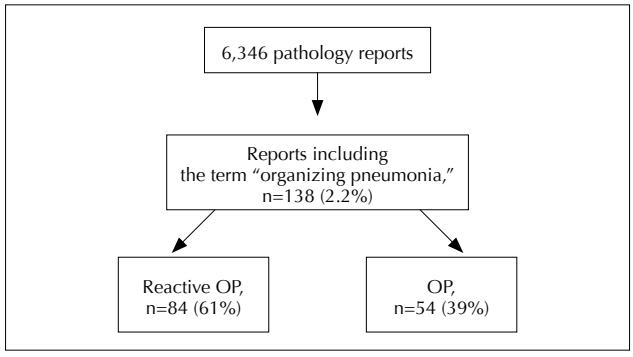


Figure 1. Flowchart of patients

Table 1. Diseases in which reactive organizing pneumonia lesions are detected

Diagnosis	Number of patients
Malignancy	55
NSCLC*	40
Carcinoid tumor	7
SCLC	1
Schwannoma	1
Undifferentiated tumor	2
Malignant epithelial tumor	1
Lymphoma	1
Fibrosarcoma	1
Large cell lung cancer	1
Infections	13
Lung abscess	4
Pneumonia	4
Cyst hydatid	2
Tuberculosis	2
Aspergillus	1
Interstitial lung disease	6
Hypersensitivity pneumonia	3
Usual interstitial pneumonia	1
Cellular non-specific interstitial pneumonia	1
Bronchiolitis	1
Bronchiectasis	4
Bulla	2
Foreign body	1
Hamartoma	1
Bronchogenic cyst	1
Bronchopleural fistula	1

*: squamous cell lung cancer: n=25, adenocarcinoma: n=9. SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer

MATERIAL AND METHODS

The was a single-center, retrospective, observational study.

Our hospital is a chest diseases and chest surgery training and research hospital. For this study, 6,346 pathology reports written in our hospital between January 2011 and January 2015 were reviewed, and 144 patients who were diagnosed with OP were examined (Figure 1). In the first 2 years of the study, lung transplantation was performed at our clinic. Six OP patients undergoing lung transplantation were excluded because they might have changed the rate of reactive OP; thus, the remaining 138 patients were included in the study.

Clinical, laboratory, and radiological findings of the included patients were obtained from their medical records.

The patients were first defined as having reactive or primary OP:

Reactive OP: OP that is found along with a primary disease or as a minor finding of another disease.

Primary OP: OP that is found without another primary disease and not as a minor finding of another disease.

Diseases associated with reactive OP lesions and patient characteristics were recorded. The medical records of primary OP patients were examined, and these patients were divided into two groups according to their clinical findings:

Cryptogenic OP: Patients without any etiological causes.

Secondary OP: Patients developing OP secondary to another cause.

The radiological features of primary OP patients were examined in three groups [8]:

Typical: Multiple, frequently bilateral, patchy alveolar opacities.

Focal: Focal nodular or massive opacities.

Infiltrative: Interstitial involvement with small alveolar opacities.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences version 16.0 (SPSS Inc.; Chicago, IL, USA). The values are presented as mean±standard deviation.

Approval for the study was received from the Local Scientific Ethical Committee of Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was not obtained from the patients because of the retrospective design.

RESULTS

The OP pattern was detected in 138 patients (2.2%) from 6,346 reports in the pathology laboratory of our hospital between 2011 and 2015. Among the 138 patients, 34 (25%) were males and their mean age was 54±14 years (range, 16-80 years). Tissue samples from 132 patients (96%) came from surgical resection, and samples from 6 patients were taken as transbronchial biopsies.

A pathological classification found that 84 (61%) patients had reactive OP and that 54 (39%) patients had primary OP. A total of 69 (84%) reactive OP patients and 35 (65%) primary OP patients were males. The mean ages werewere 53±14 years and 54±14 years, respectively.

Table 2. General features of organizing pneumonia patients according to their radiological features

	Typical OP (n=16)	Focal OP (n=34)	Infiltrative OP (n=4)
Gender			
Male/Female	8/8	24/10	3/1
Mean age, years	51±16	53±14	59±11
Etiology			
Cryptogenic/Secondary	16/0	30/4	2/2
Involvements of lesions on performing PET-CT (SUVmax)	-	6.1±3.9 (1.7-16.7)	-

OP: organizing pneumonia, PET-CT: Positron emission computed tomography, SUVmax: maximum standardized uptake value

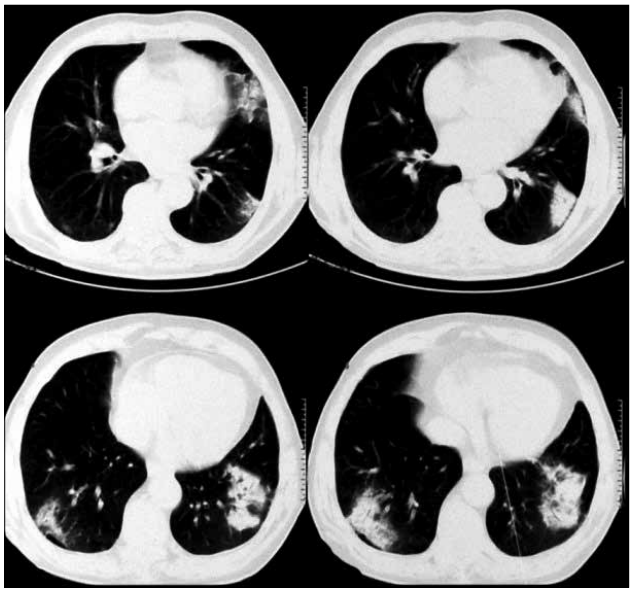


Figure 2. Typical organizing pneumonia

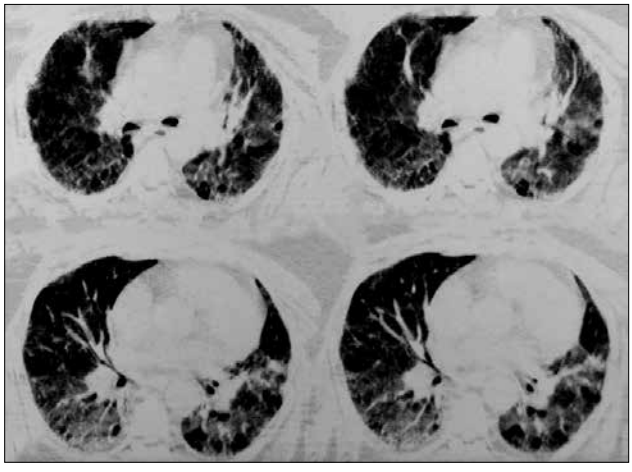


Figure 3. Infiltrative organizing pneumonia

All reactive OP lesions had been defined in surgical resection interventions. Resections had been performed in the right lung in 53 (63%) patients. Primary diagnoses of these 53 patients were mostly malignancies (n=55, 65%) and infections (n=13, 15%). Six (7%) of these patients had non-OP interstitial lung disease and four (5%) had bronchiectasis (Table 1).

Among 54 primary OP patients, 48 (89%) were diagnosed as having cryptogenic OP (COP) and 6 as having secondary OP. In 2 COP patients, the coexistence of eosinophilic pneumonia and OP was observed. The cause of secondary OP was hypersensitivity in 2 patients and connective tissue diseases in 4 patients.

The radiological findings of primary OP patients were classified as typical in 16 (30%) patients, focal in 34 (63%) patients, and infiltrative in 4 (7%) patients (Table 2) (Figures 2-8).

Eight typical OP patients were males, and their mean age was 51±16 years. All were diagnosed with COP, and the typical OP pattern in 6 patients was diagnosed through TBB.

All focal OP patients underwent surgical resection due to the suspicion of malignancy. Twenty-eight focal OP patients had undergone PET-CT, and 11 had accompanying lymphadenomegaly. The widest diameter of focal opacities was 2.7±1.2 cm (range, 1.2-4.9 cm) on average, and the SUVmax at PET-CT was 6.1±3.9 (range, 1.7-16.7).

DISCUSSION

In our study, 54 primary OP patients were evaluated, and reactive OP lesions were reported in 84 patients in the same period.

Organizing pneumonia was first defined 1983, and it was called OP due to the dominant involvement of the alveoli. Two years after that, it was named as "bronchiolitis obliterans organizing pneumonia" considering the involvement in the terminal bronchioles. However, because this term can be confused with "obliterative bronchiolitis", which leads to obstruction in small airways, only the term "organizing pneumonia" is used [1,2].

Organizing pneumonia is the most striking finding in COP. Other than OP disease, t can be seen in vasculitis, bronchocentric granulomatosis, chronic eosinophilic pneumonia, hypersensitivity pneumonia, diffuse alveolar damage, nonspecific pneumonia, lung abscess, pulmonary infarct, and cancers, but as a minor finding [9]. OP can also coexist with fibrotic interstitial pneumonia as small foci [2]. In our study, OP lesions were detected in 84 patients as a minor finding of other diseases. These lesions were mostly reported to occur with malignancy and infections (lung abscess, cyst hydatid, tuberculosis, aspergillus, etc.). Other diseases that occur with the OP pattern include hypersensitivity pneumonia, bronchiolitis and fibrotic interstitial lung diseases, bronchiectasis, bullae and foreign body, hamartoma, bronchogenic cyst, and bronchopleural fistula.

Organizing pneumonia is classified as "secondary OP" when a specific cause is detected and as "cryptogenic OP" when there is no specific cause [10]. The frequency rate of the disease is similar in men and women. Although it is mostly seen between the ages of 50 and 60 years, cases between the ages of 20 and 80 years can also be encountered [2,11]. In our study, there were 54 primary OP patients (88% COP) and the mean age of the patients was 54±14 years.

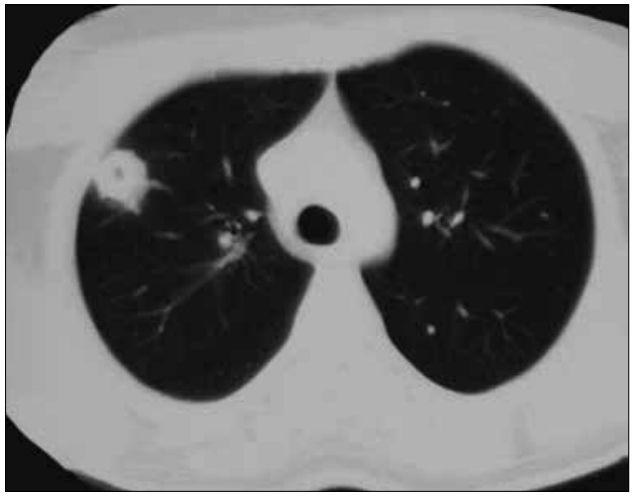
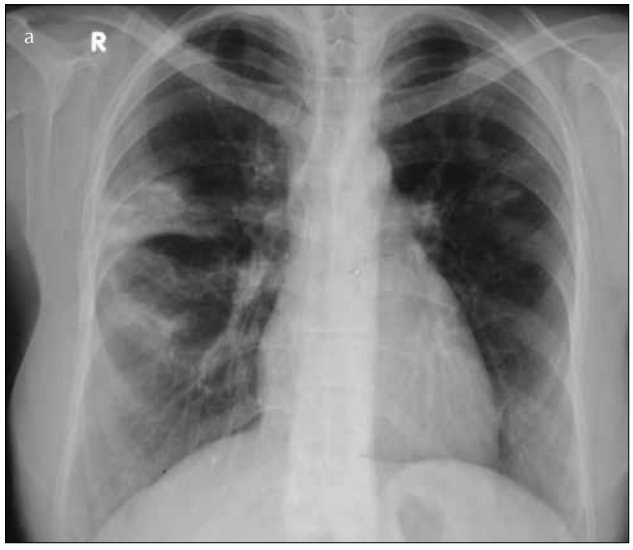


Figure 4. Focal organizing pneumonia in the right upper lobe



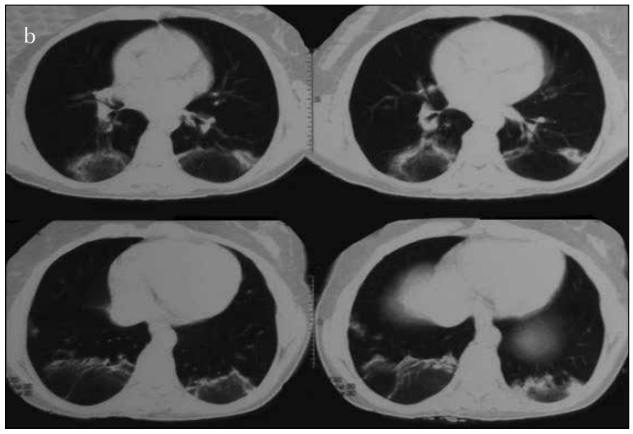


Figure 5. a, b. Typical organizing pneumonia (a). Typical organizing pneumonia (b)

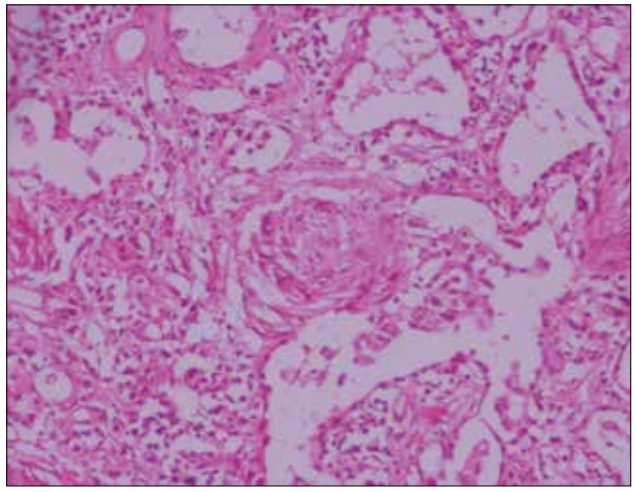


Figure 6. Histology sections that are radiologically consistent with typical organizing pneumonia (H&E, ×10)

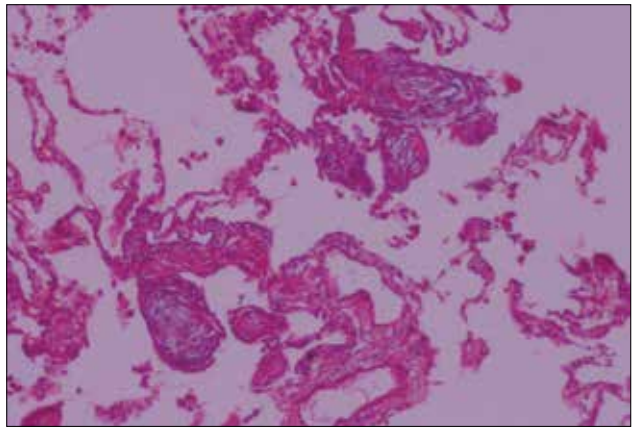


Figure 7. Histology sections that are radiologically consistent with focal organizing pneumonia (H&E, ×10)

Secondary OP can develop secondary to some causes such as heart-lung transplantation, bone marrow transplantation, infections, acute respiratory distress syndrome, drug use, radiotherapy, connective tissue diseases, hypersensitivity pneumonia, and aspiration pneumonia [5]. The series by Sveinsson et al. [6] included 58 cryptogenic OP and 46 secondary OP patients. They reported the causes of secondary OP to be infections (most commonly by *Streptococcus pneumoniae* and *Haemophilus influenza)*, drug use (amiodarone, nitrofurantoin, busulfan, and methotrexate), cancers (breast, lung, and non-Hodgkin lymphoma), connective tissue diseases (rheumatoid arthritis, polymyalgia rheumatica, and Sjögren's syndrome), and radiotherapy in 46% of their patients [6]. The causes defined in 21 secondary OP patients in the series by

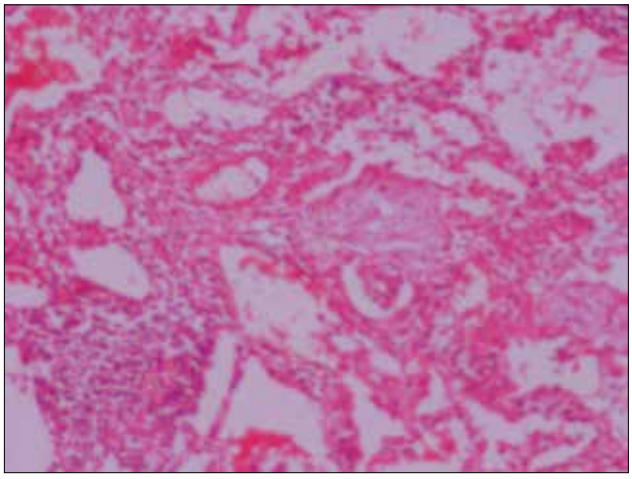


Figure 8. Histology sections that are radiologically consistent with infiltrative organizing pneumonia (H&E, ×10)

Drakopanagiotakis et al. [7] were drug use (29%), rheumatic diseases (20%), breast and colon cancers (24%), lymphoma (14%), renal transplantation (5%), and infections (9%). The frequency of OP was reported to be 2%-4.8% in rheumatoid arthritis patients [12]. In our series, the fact that the number of secondary OP patients was lower than that of COP patients might have resulted from the fact that patients with comorbid diseases less frequently applied to our hospital as ours is a chest diseases hospital. The causes in 6 secondary OP patients were hypersensitivity and connective tissue diseases that were newly diagnosed after investigating the etiology of OP in our study.

Surgical resection or TBB is required for making a diagnosis [13]. The samples in our series were mostly surgical resection materials, and all patients diagnosed through TBB had typical OP radiological findings.

The radiological appearance is frequently multifocal alveolar consolidation with peripheral localization. A reversed halo sign is found at the rate of approximately 20%, and it is indicative of OP [9,14]. It can also appear as a diffuse bilateral infiltration or solitary focal mass lesion [11]. In our study, radiological findings of 54 patients were found to be more consistent with focal OP and less consistent with the infiltrative type.

In lesions occurring as a solitary opacity, OP can also mimic lung cancer by displaying high FDG involvement such as inflammation, granulomatous infections, benign tumors, and autoimmune diseases [3,15]. In the literature, it has been observed that radiological features and metabolic activities of focal OP patients are not enough to rule out a malignancy, and these patients frequently undergo surgery for making a diagnosis [16]. In our series, high FDG involvement at the malignancy level drew attention to focal OP patients, and these patients were mostly operated on due to the suspicion of malignancy. FDG involvements in patients were observed in a range from 1.7 to 16.7. According to our research, there have been no clinical studies on this issue. It was thought that different metabolic activities were been detected in lesions in association with the inflammation stage in OP.

Maldonado et al. [5] evaluated 26 focal OP patients who were diagnosed through surgical biopsies over 8 years. The median age of the patients was 66 years (range, 36-96 years); 42% of the patients were females, and 27% were active smokers. Involvement was reported in all 11 patients who underwent PET, while they were asymptomatic at the time of diagnosis. A history of malignancy and active malignancy was reported in 6 patients. It is specified that irregularity and spiculation could be radiologically observed in lesions, including nodular, massive, and focal consolidation. Three of these 6 cases were evaluated to be secondary to infection, and the others were evaluated to be cryptogenic [5]. Yang et al. [17] reported the involvement of focal OP lesions on performing contrast-enhanced CT. On the other hand, Melloni et al. [18] reported the presence of involvement on performing PET imaging for localized OP defined in 4 patients. In our series, focal OP was detected in 34 patients. Among them, 29% were females and their mean age was 53 years. In PET-CT, SUVmax values showed involvement between 1.7 and 16.7.

In conclusion, OP is found as a minor histological finding with diseases other than OP in pathology reports. An etiological cause is often not found in OP patients. Cryptogenic and radiologically focal OP are more frequently encountered. Focal OP lesions are generally detected in surgical resections with a pre-diagnosis of malignancy.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital.

Informed Consent: Written informed consent was not obtained from the patients because of the retrospective design.

Peer-review: Externally peer-reviewed.

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ORIGINAL ARTICLE

An editorial comment on this article is available at page 65.

A Study Examining Compliance with the Anti-Tobacco Law Nb. 4207 Inside Taxis

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Abstract

OBJECTIVES: This observational study assessed compliance with the anti-tobacco Law Nb 4207 with regard to taxis in Çankaya district, Ankara.

MATERIAL AND METHODS: This descriptive study was conducted in Kızılay, Kuğulu, and Tandoğan intersections on January 18-23, 2016 between 9.00-11.00 and 14.00-16.00 hours in Ankara. Data regarding the status of the taxi (either cruising or not), smoking inside taxis, smoking status of the taxi drivers and/or clients, location of the clients in the taxi, presence of a child in the taxi, and status of the windows (open or not) were recorded using a data-gathering form.

RESULTS: Three thousand six hundred fifty-six taxis were evaluated, of which 79 (2.2%) taxi drivers were observed smoking. Clients were observed smoking in 17 taxis (1.3%). Ninety-four taxi drivers and/or clients (2.6%) were observed smoking. Taxi drivers smoked more frequently in the absence of a client. In addition, a smoking client influenced the taxi driver's smoking status ($p<0.001$).

CONCLUSION: Violation of the anti-tobacco Law Nb 4207 was observed. In this regard, the number of inspections needs to be increased. Systematic training programs for the taxi drivers regarding the risks of tobacco should be a priority. Preventive studies concerning the hazards of passive smoking should be also conducted at a community level.

KEYWORDS: Tobacco, policy, smoke-free, taxi, compliance

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INTRODUCTION

Tobacco use is one of the most important health problems worldwide. The World Health Organization (WHO) has defined smoking as biological, sociological, and psychological poisoning [1].

Approximately 1.5 billion people worldwide use tobacco. In Turkey, 14.8 million people (27.1%) use tobacco and tobacco products. Among these, 94.8% smoke cigarettes. According to a report prepared by the Turkish Statistical Institute in 2012, the prevalence of smoking in males was 41.4% and 13.1% in females [1]. In previous studies, it has been found that drivers, police officers, and press members were those who smoked the most; three-fourths (74.3%) of intercity bus drivers and two-thirds of police officers and press members were found to be smokers [2].

The harmful effects of the use of tobacco and tobacco products on human health have been known for many years. Every year, approximately six million people worldwide die from tobacco use. If this situation is not brought under control, it is estimated that the number of deaths will reach eight million by 2030 [3]. Every year, tobacco use causes more deaths than the total number of deaths caused by Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS)/, substance abuse, alcohol use, traffic accidents, and gunshot wounds [4].

Tobacco use has serious adverse effects on health as well as the environment and economy. In a smoking environment, the quality of indoor air deteriorates; in this way, nonsmokers are passively influenced and harmed by cigarette smoke [5]. This situation is also referred as "passive smoking" or "secondhand smoke" [6]. According to the estimates of the WHO, there are more than 600,000 deaths per year due to passive smoke exposure [7]. There has been an increasing amount of information suggesting that harm due to smoking is not limited to only smokers and that the risk of cancer, cardiovascular diseases, and stroke-related mortality increases in those who are passively exposed to smoke [5]. Many different groups of people are under risk of passive smoke exposure. These risks are more prevalent in places that are open to the public, houses, public transportation vehicles, and taxis [5]. Violations of the Law No. 4207 on "the Prevention and Control of the

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Hazards of Tobacco Products" are encountered in everyday life in public transportation vehicles and taxis [2]. According to the results of a survey in which 135 taxi drivers participated in Ankara in 2008, it was found that 59.3% of the drivers were smokers and that they mostly smoked in taxis [2].

Struggle with tobacco use and passive smoking is an important issue in health promotion [8]. The prevention of health-threatening risks is also an important public responsibility to ensure that both the individual and the community remain at the highest level of health [9]. Due to this responsibility, it is necessary to prevent smoking in taxis and to fully comply with Law No. 4207 [10].

Considering all these reasons, this study aimed to determine whether smoking is allowed in moving vehicles and at the red light and to determine whether there is a difference among vehicles that are moving and those that are at the red light in terms of the smoking status in the province of Çankaya, Ankara.

MATERIAL AND METHODS

Type of Research
This research is a descriptive, epidemiological study.

Variables of the Study
The independent variables are smoking in the taxi (smoking status of the taxi driver and smoking status of the customer/passenger, if any). The defining variables are the presence of a customer in the taxi, the presence of children in the taxi, whether the taxi driver uses the mobile phone in the taxi, whether the windows of the taxi are open or closed, and the place where the customer was seated in the taxi.

Source and Collection of Data
Observations made on taxis at certain hours at the intersection formed the data source.

Ethical Issues
Ethics committee approval was not required and obtained for two basic reasons. First, the study was conducted on a purely observational basis far from the objects using a check list. Second, the object of the study was "taxi" and in this sense, there was no communication/contact with the people inside the taxis and no personal data about the individuals were collected. Data obtained from the research were not used except for the study purpose. When the observation was made, descriptive properties such as the license plate and cigarette brand were not recorded.

Statistical Analysis
The information in the data sheets that were prepared was analyzed using IBM Statistical Package for the Social Sciences 21.0 (IBM Corp. Released 2012; IBM SPSS Statistics for Windows, Armonk, NY, USA, Version 21.0, Provided by Hacettepe University Libraries). Frequency and percentage distributions were obtained from the statistical analysis, and the chi-square test was used for the comparison of groups.

Universe and Sample of the Research
The universe of the research was constituted by taxis passing Ziya Gökalp street between January 18th and 19th 2016 in Çankaya, Ankara; taxis passing the Kuğulu intersection between January 20th and 22nd 2016; and taxis passing the Tandoğan intersection on January 23rd 2016 at 09:00-11:00 and at 14:00-16:00. Sixty-three taxis in which the smoking status of the driver, the presence of a customer, the smoking status of the customer, the place where the customer was seated in the taxi, and the presence of a child in the taxi could not be fully assessed were excluded from the survey. As a result, analyses were conducted on 3656 taxis (Figure 1).

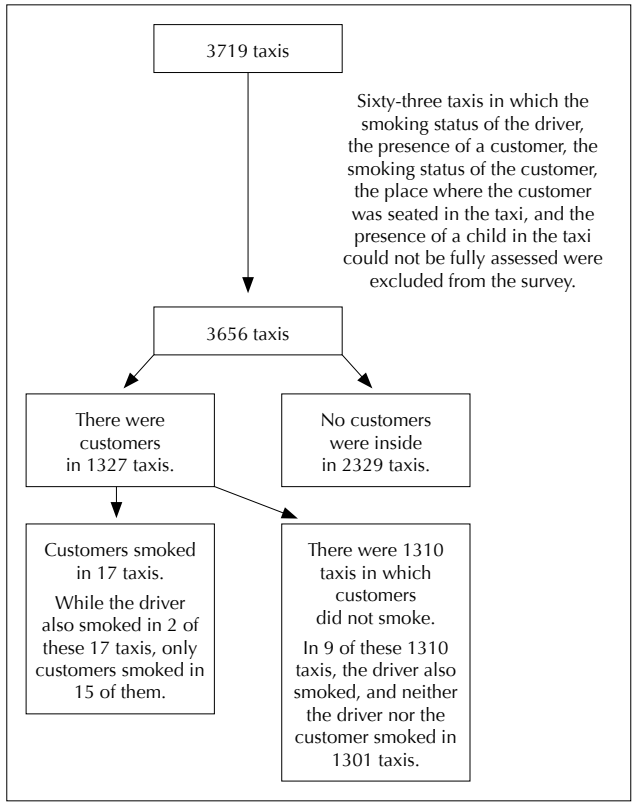

Figure 1. Flowchart for the observations

Figure 2. Picture of the start of the Kızılay Square-Ziya Gökalp street

Location of the Research
The research was performed at certain intersections in the Çankaya province of Ankara. These intersections are Kızılay Square-Ziya Gökalp Street, Kuğulu intersection-Atatürk Boulevard, and Tandoğan intersection-Dögol Street.

A photograph of the start of Kızılay Square-Ziya Gökalp Street is shown in Figure 2. Taxis waiting and/or moving at the red light were observed on both sides of the street.

Figure 3. Picture of the Kuğulu intersection

Figure 4. Picture of Tandoğan Intersection Dögol Street

A photograph of the Kuğulu intersection is shown in Figure 3. Taxis from the direction of Kızılay to the Kuğulu intersection and taxis that were moving in the direction of Kızılay from Kuğulu Park were observed.

A photo of the Tandoğan intersection from Dögol Street is shown in Figure 4. Taxis were observed in both directions from the side of Dögol Street that is seen in the figure (from the Anatolian Station of Ankaray).

Definitions and Criteria

Passive cigarette smoke exposure: It is the composition of smoke that a smoker blows out and the smoke that comes from the tip of burning cigarettes or other tobacco products. In Turkey, second-hand smoke or passive smoke exposure is also used instead [11].

Taxi: It is a class M1 motor vehicle that has a maximum of nine seats including the driver [12].

Law No. 4207: The Law on the Prevention and Control of the Hazards of Tobacco Products [13]

Manpower for the Research

Five final year students studying at the Public Health Department of Hacettepe University and faculty members and research assistants working at the Public Health Department of the Hacettepe University Faculty of Medicine comprised the manpower.

Table 1. Some characteristics of vehicles (January 18th to 23rd 2016, Ankara)

Characteristic	Number	%
Vehicle route (n=3656)		
Tunalı-Kızılay	886	24.2
Kızılay-Tunalı	831	22.7
Kolej-Kızılay	754	20.6
Kızılay-Kolej	568	15.5
Tandoğan-Kızılay	327	8.9
Kızılay-Tandoğan	290	7.9
Time when making the observation (n=3656)		
09.00-11.00	1800	49.2
14.00-16.00	1856	50.8
Status of the taxi (n=3656)		
Moving	2826	77.3
At the red light	830	22.7
Presence of a customer in the taxi (n=3656)		
Yes	1327	36.3
No	2329	63.7
Place where customers are seated in the taxi (n=1327)		
Front seat	369	27.8
Rear seat	855	64.4
Front and rear seats	103	7.8
Presence of children in the taxi (n=1328)		
Yes	93	7.0
No	1235	93.0
State of the windows at the time of making the observation (n=3637) [1]		
Open	563	15.5
Closed	3074	84.5

[1]The state of the windows could not be assessed in 19 vehicles

RESULTS

Some of the characteristics of the taxis, the smoking status in the vehicles, and some factors related to the smoking status are presented within the context of the research findings.

A total of 3719 vehicles were observed between January 18th and 23rd 2016. Among the 3656 vehicles that were evaluated, 831 (22.7%) vehicles moving in the direction of Kızılay-Tunalı, 886 (24.2%) in the direction of Tunalı-Kızılay, 568 (15.5%) in the direction of Kızılay-Kolej, 754 (20.6%) in the direction of Kolej-Kızılay, 327 (8.9%) in the direction of Tandoğan-Kızılay, and 290 (7.9%) in the direction of Kızılay-Tandoğan were observed (Table 1).

In total, 1800 (49.2%) of the 3656 vehicles were observed between 09.00 and 11.00 and 1856 (50.8%) were observed between 14.00 and 16.00 (Table 1).

Table 2. The smoking status of drivers and/or customers in observed vehicles (January 18th to 23rd 2016, Ankara)

Characteristic	Number	%
Smoking status of drivers (n=3656)		
Smoking	79	2.2
Not smoking	3577	97.8
Smoking status of customers (n=1327)		
Smoking	17	1.3
Not smoking	1310	98.7
Smoking status of drivers and customers (n=3656)	2	0.1
Smoking status of drivers or customers (n=3656)	92	2.5
Nonsmoking status of drivers and customers (n=3656)	3562	97.4

Table 3. The smoking status of taxi drivers according to some observations in taxis (January 18th to 23rd 2016, Ankara)

Some observations in taxis	Smoking status of driver					
	Yes		No		Total	
	Number	%	Number	%	Number	%*
Presence of customers (n=3656)**						
Yes	11	0.8	1316	99.2	1327	36.3
No	68	2.9	2261	97.1	2329	63.7
Smoking status of customers (n=1327)***						
Yes	2	11.8	15	88.2	17	1.2
No	9	0.7	1301	99.3	1310	98.8
Presence of children in taxis (n=1328)****						
Yes	-	-	93	100.0	93	7.0
No	11	0.9	1224	99.1	1235	93.0

* Column percentage, others are line percentages.
** Chi square=17.479, p<0.001
*** Situations without customers are not included. According to Fisher's chi square test, p=0.008
**** Chi square=0.835, according to Fisher's chi square test; p=0.494

Table 4. The state of the windows being open or closed while drivers are smoking (January 18th to 23rd 2016, Ankara)

Smoking status of drivers	The state of the windows that were observed					
	Open		Closed		Total**	
	Number	%	Number	%	Number	%*
Yes	43	54.4	36	45.6	79	2.2
No	520	14.6	3038	85.4	3558	97.8
Total**	563	15.5	3074	84.5	3637	100.0

*Column percentage, others are line percentages.
**The taxis in which the state of the windows could not be determined were excluded from the assessment. Chi square=93.6, p<0.001

Totally, 2826 (77.3%) of the 3656 vehicles were observed while moving and 830 (22.7%) of them were observed at the red light (Table 1).

Seventy nine (2.2%) taxi drivers were found to be smoking in the observed vehicles. In 17 (1.3%) taxis with customers, it was observed that the customer was smoking (Table 2).

It was observed that a cigarette was smoked in 94 (2.6%) of 3656 vehicles (Table 2). While 11 drivers (0.8%) smoked in 1327 taxis with customers, 68 drivers (2.9%) smoked in 2329 taxis without customers. There was a statistically significant difference (p<0.001) between the status of whether there was a customer in the taxi and the smoking status of taxi drivers (Table 3).

In 2 (11.8%) taxis in which 17 customers were found smoking, taxi drivers were smoking cigarettes, and the drivers were not smoking in 15 taxis (88.2%). The drivers were also not smoking in 1301 (99.3%) taxis in which there were 1310 customers who were not smoking, and drivers were smoking in 9 taxis (0.7%). There was passive cigarette smoke exposure in 26 vehicles. There was a statistically significant difference between the customer's smoking status and the driver's smoking status (Fisher's chi square test, p=0.008). The taxi drivers do not smoke in almost all (99.3%) taxis in which their customers do not smoke (Table 3).

In 1317 taxis, smoking was not observed. There were 93 children observed during the study. There was no statistically significant difference between the status of smoking and the presence of children (p=0.494) (Table 3).

Among 79 drivers, 43 (54.4%) were smoking while the window was open and 36 (45.6%) were smoking while the windows were closed. The window was open in 520 (14.6%) of the 3558 taxis in which the drivers were not smoking, and it was closed in 3038 (85.4%) of them. There was a statistically significant correlation between the window being open and the smoking stats of the taxi driver (p<0.001) (Table 4).

DISCUSSION

In this study, compliance of the taxi drivers' and customers' with paragraph c of Article 2 of Law No. 4207 on the Prevention and Control of Hazards of Tobacco Products was observed at three selected intersections of Ankara [13]. Smoking frequency of drivers was found to be 2.2% (instant watch). The percentage of customers smoking inside the taxis was found to be 1.3% using the same method (Table 2). Although the laws and legal sanctions prohibit smoking in confined spaces, it was found that the law was violated. These violations may be due to the insufficiency of taxi inspections while they are moving.

Smoking in vehicles has been the subject of different studies. In a study conducted by Sullman et al.[14] in six different states in the United Kingdom, the percentage of smoking cigarettes in vehicles was found as 2.2%. They observed 7168 vehicles in their study. The study conducted by Sullman et al. [14] differs from the present study in terms of data collection methods.

One of the factors that affects the smoking frequency of taxi drivers can be the presence of a customer in the taxi. For example, while the driver's smoking frequency is 2.9% when there is no customer, it is 0.8% in the presence of a customer. The lower frequency of smoking cigarettes in taxis with customers may be due to the fact that customers feel uncomfortable with cigarette smoke

inside or due to the driver's warning in terms of "not to smoke" inside. In fact, none of the drivers were found smoking in taxis if there were children as customers. This may have been due to the fact that parents do not allow others to smoke near their children or due to the fact that drivers are more careful about smoking when there is a child in their vehicle. In addition, this situation may have been caused by the fact that the frequency of the presence of children in taxis during the observation hours was low.

In the present study, it was observed that there is a risk of passive cigarette smoke exposure in the taxis. In this study, smoking was observed in 94 (2.6%) of the 3656 vehicles (Table 2). The deterioration of the air quality in a smoking environment violates the right of other people in the environment to breathe fresh air. Similarly, in addition to the fact that smoking in a taxi is a risk of causing passive cigarette smoke exposure to other people at that moment, it deteriorates the quality of respiration of individuals who travel by taxis even after smoking ended. Therefore, 2.6% of passive cigarette smoke exposure in the present study does not reflect the passive exposure of all possible cigarette smoke because the status of smoking cigarettes before a customer takes a taxi could not be assessed. The reason why customers violate Law No. 4207 may be because they are not aware about this law. Another reason may be that the warning label indicating the legal regulations and penal consequences of not abiding with them does not exist in taxis or is not put in places that are visible to anyone [13]. Pedrol et al. [15] observed 1600 vehicles in Spain and found that the risk of passive cigarette smoke exposure was 6% among individuals under 18 years of age. Thus, all the vehicles rather than taxis were included in their study.

In the present study, there was a statistically significant difference between the smoking status and state of the windows being open or closed in taxis. It was found that the windows were more frequently open in taxis in which cigarettes were smoked (Table 4). However, the fact that the windows were open when smoking in taxis does not prevent passive cigarette smoke exposure.

Study Limitations

Although three central intersections in Ankara were considered, the frequency of smoking does not reflect the general picture in Ankara. At the same time, there were differences in traffic intensity and intensity of traffic control at selected intersections. For example, the reason for the low frequency of smoking in Kızılay may be the intensive traffic controls in this region. Another limitation is that the observations were not continuously made but at certain hours within the day; therefore, the frequency of smoking cannot be referred to the whole day. It is possible that the frequency of smoking cigarettes increases due to diminished traffic control after the evening hours and that the detection possibility of violations reduces. Negative weather conditions limited the duration of the observation.

To conclude, violation of the law Nb. 4207 was observed in this study. Therefore, it is proposed that the number of inspections should be increased so that existing violations can be identified and necessary penalties can be imposed. Efforts should be made to increase the awareness of taxi drivers about the harm of tobacco use. Efforts should also be made to increase the awareness of the community about the importance and prevention of passive cigarette smoke exposure.

Ethics Committee Approval: Ethics committee approval was not required and obtained for two basic reasons. First, the study was conducted on a purely observational basis far from the objects using a check list. Second, the object of the study was "taxi" and in this sense, there was no communication/contact with the people inside the taxis and no personal data about the individuals were collected.

Informed Consent: As no actual comminicaton/contact was provided with the people whose smoking behaviors were observed during the study, the researchers could not have the opportunity to receive informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.Ö., H.K., İ.G., B.E., Ö.S., T.Ş., D.A.; Design - B.Ö., H.K., İ.G., B.E., Ö.S., T.Ş., D.A.; Supervision - D.A.; Financial resources (for only questionnaire photocopy amount) - B.Ö., H.K., İ.G., B.E., Ö.S.; Data Collection and/or Processing - B.Ö., H.K., İ.G., B.E., Ö.S., T.Ş., D.A.; Analysis and/or Interpretation - B.Ö., H.K., İ.G., B.E., Ö.S., T.Ş., D.A.; Literature Search - B.Ö., H.K., İ.G., B.E., Ö.S., T.Ş., D.A.; Writing Manuscript - B.Ö., H.K., İ.G., B.E., Ö.S., T.Ş., D.A.; Critical Review - D.A.

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CASE REPORT

Ranitidine-Induced Anaphylaxis in a Patient with Acute COPD Exacerbation

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Abstract

Ranitidine is a well-tolerated H2-receptor antagonist commonly used in peptic ulcer treatment and stress ulcer prophylaxis. Anaphylaxis is rarely observed with ranitidine. We report the case of a patient who developed anaphylaxis after intravenous injection of ranitidine for acute COPD exacerbation. This article underlines the importance of awareness that in COPD acute exacerbation treatment, ranitidine, which is usually administered with methylprednisolone, also has anaphylaxis potential.

KEYWORDS: Drug allergy, ranitidine, anaphylaxis

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INTRODUCTION

Ranitidine is a H_2-receptor antagonist widely used worldwide for the treatment of gastroesophageal reflux, peptic ulcers, and stress ulcers prophylaxis. It has an excellent safety profile and allergic reactions to ranitidine are very rare [1]. We herein report the case of a patient with ranitidine anaphylaxis treated for acute chronic obstructive pulmonary disease (COPD) exacerbation. Diagnosis was confirmed with a typical history of anaphylaxis developing within minutes after drug injection and positive skin prick test.

CASE PRESENTATION

A 57-year-old male patient was referred to our outpatient clinic with a history of anaphylaxis. He experienced three episodes of anaphylaxis in the last 6 months and the last one was 3 months ago. He had no other disease other than COPD. Every episode occurred a short time after treatment at the emergency room for acute exacerbation of COPD. At his last admission, after co-administration of inhaler salbutamol, intravenous (iv) methylprednisolone and iv ranitidine, he developed facial swelling and hives throughout his body, red eye, worsening difficulty in breathing, and syncope. The same medicine was given and the same clinical presentation had occurred at the other two episodes as well. There was no concurrent use of antibiotics or analgesics or any suspicious food intake. His symptoms, including cough, sputum, and dyspnea, had worsened in the last 3 months; nevertheless, because of his anxiety and fear that treatment may worsen his condition, he had increased his intake of short acting beta-agonist therapy to 7-8 times a day in addition to his stage-D COPD therapy (salmeterol/fluticasone 50/500 2 × 1, tiotropium bromide 18 mg/day, theophylline 300 mg/day) and refused admission to any hospital. He had no history of atopia or drug allergy, neither did his family. Since the allergic reaction started within minutes of co-administration of acute exacerbation treatment drugs, and this event had occurred three times, the reaction was considered to be secondary to ranitidine or methylprednisolone. Skin tests with ranitidine (Ulcuran®; 25 mg/mL) and methylprednisolone (Prednol®; 20 mg/mL) were performed. Direct prick tests and intradermal (1:10 diluted and direct) tests with methylprednisolone were negative. Direct prick test with ranitidine revealed a 10 × 9 mm weal surrounded by erythema, and the test was considered positive (Figure 1). Oral provocation (OP) tests with methylprednisolone and esomeprazole were also performed with ranitidine positivity taken into consideration. Alternative safe drugs were identified and COPD treatment regimen was rearranged (methylprednisolone for 5 days, azithromycin for 3 days, and esomeprazole for 5 days were added to his routine COPD treatment). During his follow-up, the patient was reported to be able to get his exacerbation treatment without any problem since the safe drugs were initiated.

DISCUSSION

Ranitidine is a well-tolerated H_2-receptor antagonist commonly used in peptic ulcer and gastroesophageal reflux treatment. Its availability in both oral and intravenous forms, low toxicity, obtainability with ease, and lower price than proton

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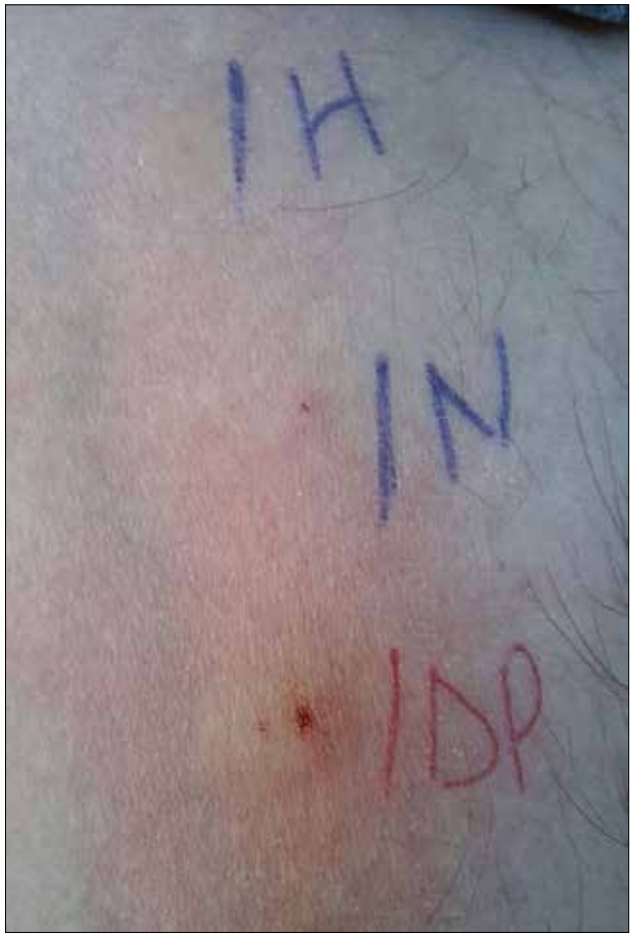

Figure 1. Direct prick test with ranitidine revealed a 10 × 9 mm weal surrounded by erythema
H: histamine; N: negative control; DP: direct prick with ranitidine

pump inhibitors has made it the drug of choice for peptic ulcer treatment and stress ulcer prophylaxis in most emergency rooms.

The patient was diagnosed with ranitidine-related anaphylaxis based on his typical history of anaphylaxis developing within minutes of drug injection, his positive skin prick test with ranitidine, and his negative skin and oral provocation tests with methylprednisolone. As ranitidine is generally well-tolerated, cases with anaphylaxis are rarely reported [1-6]. Our patient had rapidly developed reaction immediately after iv administration of the drug and showed positive reaction with prick test. These features suggest that the hypersensitivity reaction was mediated by IgE. Koh et al. [7] detected ranitidine-specific IgE in serum in a patient with anaphylaxis secondary to ranitidine. Anaphylaxis at presence of stage-D COPD and respiratory failure makes our case stand out amongst others. The anaphylaxis was so severe that the patient avoided emergency room at his following COPD exacerbations due to his anxiety about drugs in his treatment regimen.

In the literature, cross reaction between ranitidine and other H_2-receptor antagonists remains contradictory. Two cases were reported in which skin prick tests were positive for famotidine, ranitidine, and nizatidine and negative for cimetidine after anaphylaxis [8,9]. It was stated that this condition may be related to the similarity of side chains among the first three drugs. Nevertheless, cases that demonstrate no cross reaction among H_2-receptor blockers in skin tests and OP test are also present [3,7,10]. Our patient was not tested with other H_2-receptor blockers due to possible cross reactions. OP test with esomeprazole, one of proton pump inhibitors with whom a cross reaction was not expected, revealed no reactions.

We report a case of anaphylaxis due to a H_2-receptor antagonist,which is safe and commonly used in clinical practice as a part of anaphylaxis therapy. Our case underlines the importance of awareness that in COPD acute exacerbation treatment, ranitidine, which is usually administered with methylprednisolone, also has anaphylaxis potential. Thus, anaphylactic reactions that may cause mortality in severe COPD patients, such as our patient, can be prevented.

Informed Consent: Written informed consent was obtained from the patient participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.Y., M.T.; Design - İ.Y., M.T.; Supervision - İ.Y., M.T.; Data Collection and/or Processing - İ.Y., M.T.; - İ.Y., M.T.; Literature Search - İ.Y., M.T.; Writing Manuscript - İ.Y., M.T.; Critical Review - İ.Y., M.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

A Rare Case of Progressive Dyspnea and Bilateral Lung Infiltration in a Young Male

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Abstract

Pulmonary lymphangitic carcinomatosis (PLC) is defined as infiltration of the lymphatic vessels and perilymphatic connective tissue with tumor cells, which is secondary to malignancy. Therefore, it rarely appears as an initial finding preceding a diagnosis of malignancy. A 30-year-old male patient was hospitalized in our clinic with a pre-diagnosis of interstitial lung disease owing to the complaints of dry cough, progressive dyspnea, and acute respiratory insufficiency. He was diagnosed with signet ring cell carcinoma, which is a histologic subtype of adenocarcinoma, via gastroscopy, and lung involvement was consistent with PLC. Regardless of the patient age, PLC should be considered in differential diagnoses of progressive dyspnea, acute respiratory failure, and widespread interstitial lung involvement.

KEYWORDS: Progressive dyspnea, lymphangitic carcinomatosis, gastric cancer

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INTRODUCTION

Pulmonary lymphangitic carcinomatosis (PLC) is the infiltration of pulmonary lymphatic vessels and connective tissue adjacent to these vessels by malignant cells. PLC comprises 6-8% of all lung metastases. The most common underlying tumors found are those of the breast, stomach, lung, prostate, and pancreas. Irrespective of the location of the primary tumor, the prognosis is worse [1].

Involvement of the lymphatic vessels usually occurs following hematogenous seeding of the lungs. A less frequent mechanism is retrograde diffusion into the lymphatics of the mediastinal and hilar lymph nodes. Not only the central lymphatics consisting of the bronchovascular interstitium, but also the peripheral lymphatics consisting of the interlobular septa and beneath the pleura are involved. The radiologic features are similar to those of other interstitial lung diseases, which complicates a differential diagnosis. Thickening of bronchovascular bundles and interlobular septa, ground-glass opacity, pleural effusion, mediastinal lymphadenopathy, and nodular lesions are the common radiologic findings [2-5]. PLC may sometimes appear as the first finding before a diagnosis of tumor [6]. PLC is rarely reported as the first finding related to stomach tumor [7]. A 30-year-old male patient, who was diagnosed with signet cell gastric carcinoma after being admitted with PLC to the clinic and undergoing radiologic examination, is presented owing to his peculiar presentation.

CASE PRESENTATION

A 30-year-old male patient presented to our outpatient clinic with complaints of shortness of breath, dry cough, weight loss, and night sweats. His complaints had started 2 months previously with a mild dry cough, which was progressive and had been accompanied by dyspnea during the previous 2 weeks. He had lost 5 kg in weight. His general condition was moderate, he had difficulty talking, and he had an oxygen saturation of 90% on finger probe. On chest X-ray, bilateral reticulonodular infiltration was noted (Figure 1a). He was hospitalized for detailed evaluation and treatment. He did not have any other medical diseases. He had a cigarette smoking history of 5 packs/year, and he had not smoked for the previous 8 years. He was born and raised in Istanbul and had worked as an officer. He had no history of taking drugs, and he had no history of exposure to any antigen that causes hypersensitivity pneumonitis (HP). The patient was evaluated by another pulmonologist owing to complaints of dry cough. His physical examination and radiologic and spirometric findings were found to be normal, and he was referred to the internal medicine clinic (Figure 1b). Although he had no gastric complaints, owing to the unexplained etiology of the dry cough he underwent gastroscopy. The pathology results had not yet been reported at that time. He had used antibiotic treatment with amoxicillin-clavunate and clarithromycin in the previous 10 days. His brother had been diagnosed with Henoch-Schönlein purpura and his uncle had undergone treatment for pulmonary tuberculosis.

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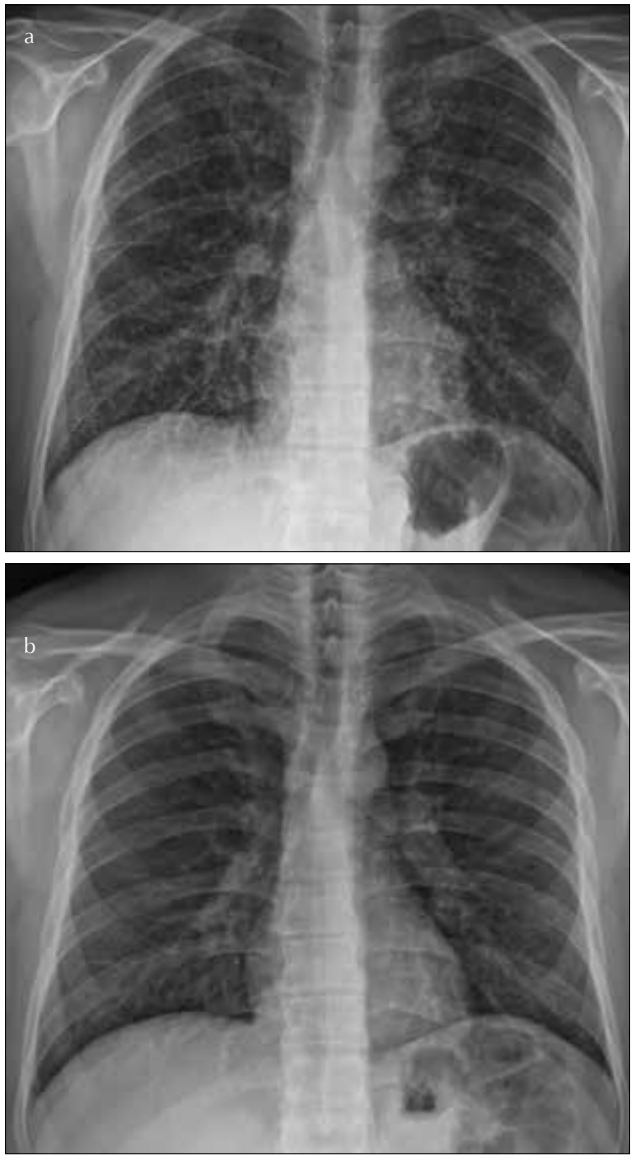

Figure 1. a, b. Chest x-ray at admission, bilateral generalized reticulonodular infiltration (a). Normal chest X-ray: 1 month before admission (b)

On physical examination, his body temperature was 36.0°C, his blood pressure was 130/80 mmHg, and his heart rate was 130/min. On complete blood count, leukocytes were 9.5/mm^3, hemoglobin was 15.4 g/dL, and platelets were found to be 160/mm^3. On routine biochemical evaluation, blood glucose was 105 g/dL and blood urea nitrogen was 83 mg/dL. Other biochemical parameters were within the normal ranges. Angiotensin-converting enzyme (ACE) was 18 U/L (normal: 66-114), D-dimer was 5 µg/mL (normal: 0-0.5), C-reactive protein was 28 mg/dL (normal: 0-5), and erythrocyte sedimentation rate was 28 mm/hr. Arterial blood gas parameters in room air were pH 7.48, $PaCO_2$ 29.9 mmHg, and PaO_2 64.7 mmHg. Despite the low levels of the infection parameters, broad-spectrum antibiotics were initiated, which consisted of piperacillin-tazobactam, ciprofloxacin, and oseltamivir, because pneumonia cannot be excluded in a young patient having progressive bilateral infiltration and progressive respiratory failure. On thorax computed tomography, minimal bilateral effusion (3 mm pleural effusion in the right hemithorax and 5 mm in the left hemithorax), generalized ground-glass opacity, and interlobular septal thickenings were identified. He had no lymphadenomegaly (Figure 2). Echocardiographic evaluation was normal. On the third day of hospitalization, his general condition worsened, his respiratory rate increased to >32/min, and his oxygen saturation decreased to 82% of that of the room air. High-resolution computed tomography (HRCT) was performed with an initial diagnosis of acute interstitial pneumonia. On HRCT, generalized ground-glass opacity, thickening of the bronchovascular interstitium, and significant interlobular septal thickenings were seen bilaterally (Figure 3). Flexible fiber optic bronchoscopy was performed for endobronchial evaluation, and a bronchoalveolar lavage (BAL) fluid sample was obtained for the pre-diagnoses of acute interstitial pneumonia and lymphangitic carcinomatosis. No endobronchial lesion was identified, and BAL was performed on the middle lobe. Transbronchial biopsy (TBB) was not performed owing to the general deterioration in the patient condition and hypoxemic respiratory failure. BAL fluid analysis revealed cell ratios of lymphocytes 24%, neutrophils 35%, and eosinophils 1%, and a CD4/CD8 ratio of 3.11. In the lavage samples, acid-fast bacilli staining was negative, *Mycobacterium tuberculosis* by polymerase chain reaction was negative, and lavage cultures did not yield any specific microorganism; galactomannan antigen was also negative. Cytological evaluation of lavage fluid reported atypical epithelial cells that suggested malignancy. Moreover, the pathology results of the gastroscopy procedure were reported as signet cell carcinoma. The radiologic findings were found to be compatible with PLC by an expert thorax radiologist. The patient was referred to the oncology clinic for a chemotherapy program.

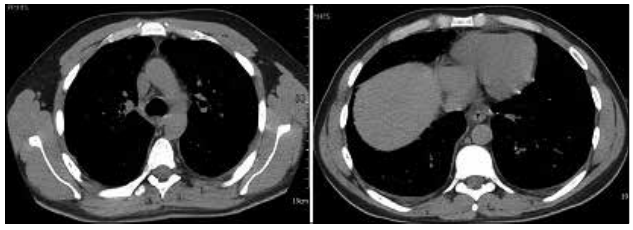

Figure 2. Thorax computered tomography: bilateral minimal effusion, no lymphadenomegaly

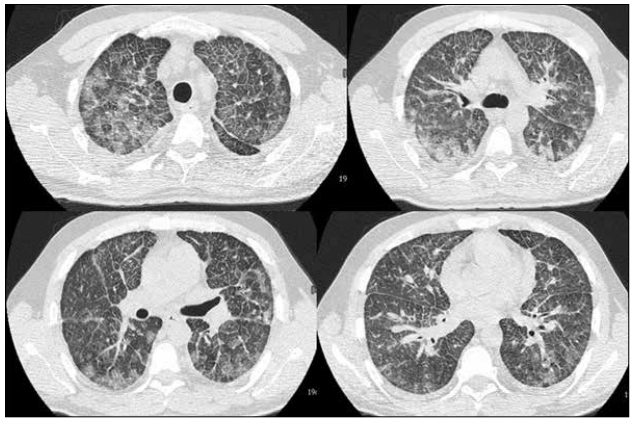

Figure 3. High Resolution Computed Tomography; bilateral ground-glass opacity and prominence of interlobular septum

DISCUSSION

The present case comprises a young male patient who was evaluated for progressive dry cough and respiratory insufficiency with a pre-diagnosis of acute interstitial pneumonia and was diagnosed with PLC due to gastric cancer. He had no gastrointestinal complaints. Thus, the present case is peculiar in its emphasis that PLC can be encountered prior to a diagnosis of malignancy at any age.

Pulmonary lymphangitic carcinomatosis was first described by Andral in a patient with uterine cancer in 1824 [8]. PLC mostly occurs secondary to malignancies of the breast, stomach, lung, prostate, and pancreas [1]. PLC may appear in the natural course of primary disease or may represent the very first finding, as in our case [7]. In nearly 50% of cases, the initial complaints are respiratory symptoms rather than symptoms of an underlying tumor. The most common clinical symptom is dyspnea, which typically starts and gradually progresses for 2-4 months before diagnosis. Dry cough often accompanies dyspnea [9].

It has been reported that 30-50% of cases have no abnormalities on chest X-ray. Therefore, for patients with a known malignancy having new-onset progressive dyspnea, HRCT is recommended as a more sensitive radiologic method [6]. HRCT findings are typically characterized by irregular and nodular thickening of the interstitial septum, subpleural nodules, prominent interstitial markings, ground-glass opacity, pleural effusion, and hilar and mediastinal lymphadenopathy [2].

Histopathologic examination is necessary for the diagnosis of PLC, but diagnosis is often made on the basis of clinical and radiologic findings because of a general deterioration in patient condition. Grenier et al. [10] reported that clinical and radiologic findings are accurate in the diagnosis of PLC in 92% of patients with diffuse interstitial pulmonary disease. Bronchoscopy should be performed in all patients who can tolerate the procedure. Cytological examination of sputum and bronchoscopic lavage, TBB, and thoracoscopic lung biopsy are the usual invasive diagnostic methods.

In a study including 31 cases, diagnoses were established by bronchial brushing, TBB, forceps biopsy, and bronchial lavage in order of frequency [11]. TBB was performed on a 24-year-old male patient similar to our case, and the pathology was reported to be metastatic carcinoma, which was thought to have originated from tumors of the stomach, pancreas, and biliary duct. This case was diagnosed as signet ring cell carcinoma by gastroscopy and whole-body magnetic resonance imaging (MRI). Whole-body MRI techniques are reported to be able to accurately identify gastric tumors, as well as liver and skeletal metastases. In addition, they are also suggested as preferable methods in patients with renal dysfunction and contrast allergy [7].

Interstitial pulmonary diseases and infectious diseases were considered as preliminary diagnoses in our case because of the patient's young age and clinical findings with acute and progressive onset. For the differential diagnosis of PCL, sarcoidosis, hypersensitivity pneumonia, vasculitis, pulmonary alveolar proteinosis (PAP), viral pneumonia, lymphoma, pulmonary edema, and Kaposi's sarcoma should be considered [6]. In the present case, sarcoidosis was not considered because of the low levels of ACE, and the CD4/CD8 ratio on BAL analysis also did not suggest mediastinal lymphadenopathy. HP was not considered because the patient had no exposure suggestive of HP and the lymphocyte levels in BAL fluid were low. Vasculitis was not thought probable because his urine test analysis, renal test function, and acute-phase reactants were not increased. The BAL findings were not compatible with PAP. No response could be observed to broad-spectrum antibiotic therapy, and the fact that no mediastinal or peripheral lymphadenopathy was present rendered a diagnosis of lymphoma unlikely. Although his clinical complaints were compatible with tuberculosis, the HRCT findings were not suggestive of tuberculosis. His sputum and BAL fluid samples did not reveal any bacilli.

Bronchoscopy and BAL were performed in the present case, but TBB could not be performed owing to the deterioration in the patient's general condition, and atypical cells were seen on lavage pathology. Moreover, the pathology results of the previously performed gastroscopy were reported as signet ring cell carcinoma. Gastric tumors are the second most common cancers in males in Turkey and worldwide [12,13]. They constitute 7.4% of cancers in males in Turkey [12]. Their incidence increases with age, mostly during the sixth and seventh decades [13].

Signet ring cell carcinoma is a histologic subtype of gastric adenocarcinoma. This pathologic subtype of stomach tumor is an independent risk factor for a more severe prognosis. Signet ring cell carcinoma is prone to infiltrate the peritoneum and lymph nodes [14].

Owing to the gradual deterioration in the general condition of our patient, further imaging could not be carried out for the investigation of distant organ metastasis, and he was transferred to the oncology clinic in order to receive chemotherapy.

In conclusion, in the presence of chronic cough, progressive dyspnea, and lesions similar to interstitial lung disease in a patient previously diagnosed with cancer, a diagnosis of PLC should be considered among the preliminary diagnoses. We should still consider a diagnosis of PLC even though the patient is young. In these cases, it should be kept in mind that respiratory complaints and findings can be seen first rather than symptoms of the primary tumor. Diagnosis can be made clinically and radiologically if a biopsy cannot be performed via bronchoscopy because of the general condition of the disorder.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.A., F.T.A., T.S.; Design - M.A., F.T.A., T.S.; Supervision - T.S.; Resources - M.A., F.T.A.; Materials - M.H., O.A.; Data Collection and/or Processing - M.A., A.S., M.H., O.A.; Literature Search - M.A., T.S., C.A.; Writing Manuscript - M.A., F.T.A., T.S.; Critical Review - T.S., C.A.; Other - M.H., O.A., A.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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