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Pulmonary alveolar proteinosis in Turkey: a review of twenty four cases

Türkiye'de pulmoner alveoler proteinozis: Yirmi dört olgunun gözden geçirilmesi

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Background: This study aims to investigate the overall characteristics of the patients with pulmonary alveolar proteinosis (PAP) in Turkey.

Methods: Between January 1958 and July 2010, national and international databases were scanned to reach articles on PAP in Turkey and full texts were reviewed. Demographic characteristics of patients, clinical data, laboratory findings, imaging studies, diagnostic methods and treatments were recorded.

Results: Twenty-two articles reporting 24 cases were found in the literature. The mean age was 21±14 years (range, 1 day to 47 years). Thoracic computed tomography revealed crazy paving appearance in nine patients, ground glass appearance in five patients, and infection in two patients. Nine patients underwent transbronchial biopsy (TBB), while 10 underwent open lung biopsy (OLB). Diagnosis was based on autopsy in three cases, bronchoalveolar lavage fluid (BALF) in two cases, TBB in four cases, OLB in nine cases, BALF and TBB in three cases, BALF and electron microscopy (EM) in one case, BALF, EM and TBB in one case, and BALF, EM and OLB in one case. Whole lung lavage was performed on six cases, while four cases underwent segmental bronchial lavage. One case was treated with intravenous immunoglobulin, while one case was treated with granulocyte colony stimulating factor. Five cases died during hospitalization. Chest X-ray revealed improved hypoxia in four cases, improved lung function test results in three cases and regressed lesions in five cases.

Conclusion: Our study results suggest that diagnostic and management approaches for Turkish patients with PAP are consistent with the published materials in the literature.

Key words: Diagnosis; pulmonary alveolar proteinosis; therapy; Turkey.

Amaç: Bu çalışmada, Türkiye'deki pulmoner alveoler proteinozis (PAP) olgularının genel karakteristik özellikleri araştırıldı.

Çalışma planı: Ocak 1958 - Temmuz 2010 tarihleri arasında ulusal ve uluslararası veri tabanları taranarak Türkiye'den yayımlanan PAP olguları incelendi ve tam metinleri gözden geçirildi. Hastaların demografik özellikleri, klinik verileri, laboratuvar bulguları, görüntüleme çalışmaları, tanı yöntemleri ve tedavileri kaydedildi.

Bulgular: Literatürde 24 olguyu bildiren 22 makaleye ulaşıldı. Ortalama yaş 21±14 yıl (dağılım, 1 gün-47 yıl) idi. Toraks bilgisayarlı tomografi incelemesinde dokuz olguda kaldırım taşı görünümü, beş olguda buzlu cam görünümü ve iki olguda enfeksiyon var idi. Dokuz olguya transbronşiyal biyopsi (TBB), 10 olguya açık akciğer biyopsisi (AAB) uygulandı. Üç olgunun tanısı otopsi ile, iki olgunun bronkoalveoler lavaj sıvısı (BALS) ile, dört olgunun TBB ile, dokuz olgunun AAB ile, üç olgunun BALS ve TBB ile, bir olgunun BALS ve elektron mikroskobu (EM) ile, bir olgunun BALS, EM ve TBB ile, bir olgunun BALS, EM ve AAB ile konuldu. Altı olguya tüm akciğer, dört olguya segmental bronş lavajı uygulandı. Bir olgu intravenöz immünoglobulin, bir olgu granülosit koloni uyarıcı faktör ile tedavi edildi. Beş olgu hastane yatışı esnasında kaybedildi. Dört olgunun hipoksisinde, üç olgunun solunum fonksiyon testlerinde, beş olgunun akciğer grafisindeki lezyonlarda düzelme görüldü.

Sonuç: Çalışma bulgularımız, Türkiye'de de PAP hastalarının tanı ve tedavisi yaklaşımlarının literatürdeki basılı yayınlarda bildirilenler ile uyumlu olduğunu göstermektedir.

Anahtar sözcükler: Tanı; pulmononer alveoler proteinozis; tedavi; Türkiye.

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Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disease characterized by the accumulation of surfactant in the alveoli. The deposition is due to the defective clearance of the surfactant by the alveolar macrophages. Diagnosis can be carried out with periodic acid-Schiff staining of the bronchial lavage fluid. Open lung and transbronchial biopsies can be used as well, although these are usually not necessary. Pulmonary alveolar proteinosis may be asymptomatic or present with dyspnea, cough, chest pain, or weight loss. Although physical examination results are often normal, cyanosis, clubbing, and rales at auscultation may be observed.[1] Bilateral alveolar infiltrations may also be seen on chest X-ray. In addition, ground glass opacities, crazy-paving appearance, and septal thickening are frequently seen in PAP cases on computed chest tomography (CT). Whole lung lavage (WLL) has been used in treatment of symptomatic patients for 50 years, but granulocyte macrophage colony-stimulating factor (GM-CSF) therapy has recently been used as an alternative.[2] This article reviews the PAP cases that have been reported in Turkey by comparing their characteristics, laboratory results, treatment, and outcomes.

PATIENTS AND METHODS

We searched the databases of The Turkish Academic Network and Information Center (ULAKBIM), Turkish Medline, PubMed, and the ISI Web of Knowledge using the term "pulmonary alveolar proteinosis" limited to "human" and evaluated all of the PAP cases on record in Turkey between January 1958 and July 2010. The full texts of the articles were reviewed by two experienced pulmonary disease specialists and a radiologist, and the patients' demographic information, clinical data, laboratory findings, imaging studies, diagnostic methods, and treatments were recorded. In order to not re-report any cases, the study investigators contacted the authors of the related manuscripts.

RESULTS

Demographics

We uncovered 22 full text articles reporting 24 cases (17 males, 7 females; mean age 21±14 years; range 1 day to 47 years) (Table 1).[3-24] These cases involved three farmers, two welders, two housewives, two office workers, and one salesman. Seven of the cases had a smoking history. The first of these cases was reported in 1964 and featured 18 and 20-year-old male patients who had been hospitalized in 1959 and 1960 (Table 2).[3]

Symptoms

Dyspnea was observed in 23 of the cases, cough in 17, fever in nine, sputum in five, chest pain in three, weight loss in three, leg swelling in two, and hemoptysis

Table 1. The list of pulmonary alveolar proteinosis cases reported from Turkey

Author	Publication
Görpe et al.[3]	Tıp Fak Mecm 1964;27:72-9
Özdemir et al.[9]	Solunum Hastalıkları 1991;2:55-60
Şimşek et al.[10]	Turkiye Klinikleri J Med Sci 1992;12:250-3
Baran et al.[11]	Solunum 1994;19:688-92
Köktürk et al.[12]	Turkish Respiratory Journal 2000;1:68-72
Kaçar et al.[13]	Tüberküloz ve Toraks Dergisi 2000;48:162-6
Ulukavak Çiftçi et al.[14]	Solunum Hastalıkları 2001;12:71-4
Seyfikli et al.[15]	Turkish Respiratory Journal 2001;2:36-9
Gülsüm et al.[16]	Bilgisayarlı Tomografi Bülteni 2002;7:38-40
Polat et al.[17]	İzmir Göğüs Hastanesi Dergisi 2003;17:73-7
Pamuk et al.[8]	Leuk Lymphoma 2003;44:871-4
Meşe et al.[6]	Türkiye Ekopatoloji Dergisi 2003;9:81-4
Sazak et al.[18]	GKD Anest Yoğ Bak Dern Derg 2003;9:77-81
Hızarcıoğlu et al.[4]	Ege Ped Bül 2003;10:151-4
Sancak et al.[19]	Yoğun Bakım Dergisi 2004;4:195-9
Gavaf et al.[40]	İzmir Göğüs Hastanesi Dergisi 2007;21:41-6
Edis et al.[21]	Ann Acad Med Singapore 2007;36:871-2
Uyar et al.[22]	Tur Toraks Der 2008;9:177-80
Patiroglu et al.[7]	Pediatr Pulmonol 2008;43:710-3
Tutar et al.[23]	Solunum 2009;11:43-5
Dogru et al.[5]	J Clin Anesth 2009;21:127-30
Yildiz et al.[24]	Respiratory Medicine CME 2010;3:267-9

Table 2. Demographic information of the Turkish patients with pulmonary alveolar proteinosis

	n	%	Mean±SD	Range
Age			21±14	1 day-47 years
Gender				
Males	17	71		
Females	7	29		
Smoking				
Smokers	7	29		
Nonsmokers	9	38		
Unknown	8	53		
Toxic particle inhalation				
Asbestos	1	4		
Welding smoke	2	8		
Agricultural particles	3	13		
Comorbidities				
Amyloidosis	2	8		
Nephrotic syndrome	1	4		
Bronchiectasis	1	4		
Hematological disorders	1	4		
Immune deficiency	1	4		

SD: Standard deviation.

in one. The median symptom duration time was five months (range five minutes to 48 months).

Physical examinations

Fourteen cases had crackles at the lung bases, 12 had cyanosis, four had clubbing, four had subcostal retractions, two had lower extremity edema, and one had hepatosplenomegaly. However, normal results were reported in four of the cases on physical examination.

Misdiagnosis and comorbidities

Seven cases had received antituberculous treatment before the diagnosis of PAP, but none had a proven microbiology for acid-fast bacilli (AFB). In addition, sputum smears for AFB were examined in 14 cases during hospitalization, and none had positive results. Five cases were diagnosed with unresolved pneumonia, and one case had idiopathic pulmonary fibrosis. Interstitial lung disease was also detected before the diagnosis of PAP in one of the cases. Furthermore, one had been exposed to welding smoke and one to both asbestos and welding smoke. Agricultural particles were also found in three of the cases while one had previously undergone a lobectomy due to bronchiectasis and unresponsiveness to antituberculous treatment. There was also one case of amyloidosis, one with a combination of amyloidosis and nephrotic syndrome, one with acute lympocytic leukemia (ALL), and another with agammaglobulinemia.

Laboratory findings

Five of the cases had normal laboratory findings, but no details were reported. However, we were able to obtain the detailed laboratory results in 10 of the cases. The mean white blood cell (WBC) count was 10,750±1,061 (range 5,100 to 15,200), the erythrocyte sedimentation rate (ESR) was 53±42 mm/hr (range 5 to 130 mm/hr), and the lactate dehydrogenase (LDH) level was 1,001±107 U/L (range 401 to 3,283 U/L). Fourteen of the 15 cases had hypoxia on arterial blood gas analysis. Diffusing capacity of the lung for carbon monoxide (DLCO) tests were conducted on six of the cases, with three reporting severe results, two moderate, and one mildly diminished. Spirometry was performed on 13 cases. Four had mild reduction, three moderate, and four had severe reduction on pulmonary function tests (PFTs) with a restrictive pattern. The results were as follows: mean FEV_1 (%): 76.5±14.7 (range, 52-101%), mean FVC (%): 58.5±17.5 (range, 50-99%), and mean FEV_1/FVC (%): 89.3±5.9 (range, 80-99.5%) (Table 3).

Radiology

Twenty-three cases underwent chest-X rays, and bilateral infiltrations were reported in all of them. Eleven cases had diffuse, nine had perihilar, and three had dominant consolidations in the lower lung zone. In addition, 16 of the cases underwent chest computed tomography (CT), and all of them had bilateral findings. Nine cases had crazy-paving patterns, five had ground glass appearance and two had concurrent infection findings. (Table 3).

Diagnosis

Fiberoptic bronchoscopy (FOB) was performed on 14 cases, and bronchoalveolar lavage fluid (BALF) analysis were performed on all of them. Electron microscopy (EM) was also performed on four of the cases, nine cases underwent transbronchial biopsy (TBB), and 10 had an open lung biopsy (OLB). The diagnosis of PAP was done by autopsy in three cases, BALF in two, TBB in four, OLB in nine, BALF and TBB in three, BAL and EM; BALF, EM and TBB; BALF, EM and OLB; each combination in single cases (Table 4).

Treatments

Six cases underwent WLL, and four underwent segmental bronchial lavage. Furthermore, one case was treated with intravenous immunoglobulin (IVIG) and another with granulocyte colony stimulating factor (G-CSF) (Table 4).

Table 3. The symptoms along with the physical examination, laboratory, and imaging findings of the Turkish patients with pulmonary alveolar proteinosis

	n	%	Median	Range
Symptoms	24	100		
Dyspnea	23	96		
Cough	17	71		
Fever	9	38		
Sputum	5	21		
Chest pain	3	13		
Weight loss	3	13		
Leg swelling	2	8		
Hemopthysis	1	4		
Duration of symptoms			5	0-48
Physical examination	24	100		
Normal	4	17		
Crackles at lung bases	14	58		
Cyanosis	12	50		
Clubbing	4	17		
Subcostal retractions	4	17		
Lower extremity edema	2	8		
Hepatosplenomegaly	1	4		
Laboratory tests				
Biochemical and blood analysis	24	100		
Normal	5	21		
Abnormal	19	79		
Arterial blood gas	15	100		
Hypoxia	14	93		
Spirometry	13	100		
Normal	2	15		
Mild reduction	4	31		
Moderate reduction	3	23		
Severe reduction	4	31		
Diffusing capacity for carbon monoxide	6	100		
Mild reduction	1	17		
Moderate reduction	2	33		
Severe reduction	3	50		
Lactate dehydrogenase	16	100		
Normal	6	63		
Elevated	10	37		
Sedimentation rate	18	100		
Normal	6	33		
Elevated	12	67		
Chest X-ray	23	100		
Diffuse consolidations	11	48		
Perihilar consolidations	9	39		
Lower lung zones dominant consolidations	3	13		
Chest CT appearance pattern	16	100		
Crazy paving	9	56		
Ground glass	5	31		
Superposition of infection	2	13		

CT: Computed tomography

Outcomes

Five cases died during hospitalization, and four had improved hypoxia in blood gas analysis. Three of the cases also had improved lung function test results while five had regression of the lesions on chest X-ray.

Child cases

Four of the cases were male children who were one day, two and a half months, 13 months, and four years old. The 13-month-old boy was investigated for interstitial lung disease because his parents had a history of consanguineous marriage, and an open lung biopsy was conducted to obtain a diagnosis. Underwater closed drainage was performed, but the patient had to be intubated for respiratory insufficiency and died on the fourth day of intubation.[4]

The four-year-old boy had previously received treatment for pneumonia and tuberculosis. The diagnosis was made by OLB, and he had hypoxia

Table 4. Diagnosis, treatments, and results of the Turkish patients with pulmonary alveolar proteinosis

	n	%
Diagnostic procedures	24	100
Bronchial lavage fluid	2	8
Autopsy	3	13
Transbronchial biopsy	4	17
Open lung biopsy	9	38
Bronchial lavage fluid and electron microscopy	1	4
Bronchial lavage fluid and transbronchial biopsy	3	13
Bronchial lavage fluid, electron microscopy, and transbronchial biopsy	1	4
Bronchial lavage fluid, electron microscopy, and open lung biopsy	1	4
Misdiagnosis	24	100
Tuberculosis	7	29
Unresolved pneumonia	5	21
Idiopathic pulmonary fibrosis	1	4
Interstitial lung disease	1	4
Treatments	24	100
Whole lung lavage	6	25
Segmental lung lavage	4	17
Intravenous immunoglobulin	1	4
Granulocyte macrophage colony stimulating factor	1	4
Observation or nonspecific treatments	13	54
Outcomes	24	100
Died during hospitalization	5	21
Improved hypoxia in blood gas analysis	4	17
Improved lung function tests	3	13
Regression of lesions on chest X-ray	5	21

at hospitalization. Whole lung lavage therapy was performed 12 times during the follow-up period, and he was reported to have less oxygen dependence after the WLL therapies.[5]

The first newborn suffered from respiratory insufficiency after the 12th hour of birth. Bronchopulmonary infiltrations were observed on chest X-ray, and he died after the 73rd day of hospitalization. Pulmonary alveolar proteinosis was diagnosed after the autopsy. Even though his parents had a history of consanguineous marriage and received a genetic consultation, they had another baby boy after a year. The second newborn baby boy had respiratory insufficiency and was intubated, but he died 30 minutes after being born. An autopsy was performed, and he was also diagnosed with PAP. In addition, an increase in the number of cells expressing surfactan apoprotein A (SP-A), which could have been a sign of surfactin apoprotein B (SP-B) deficiency, was observed in an immunohistological examination of the lung tissue.[6]

DISCUSSION

Pulmonary alveolar proteinosis is a rare lung disease, first described by Rosen et al. in 1958,[25] in which surfactant phospholipids and protein content, as revealed by periodic acid-Schiff (PAS), accumulate in the alveoli. Three subtypes of PAP have been introduced: autoimmune (idiopathic or primary), secondary, and genetic (congenital). Kitamura et al.[26] identified for the first time that PAP was associated with neutralizing GM-CSF autoantibodies in a study with GM-CSF-deficient mice. They also determined that high levels of these antibodies were present in patients with autoimmune PAP, which had been previously named as an idiopathic subtype. These patients also had defects in neutrophil functions. It is known that GM-CSF plays an important role in the terminal differentiation of alveolar macrophages and that it regulates myeloid cell host defense functions. Furthermore, pulmonary alveolar macrophages clear excess surfactant, and GM-CSF has the ability to stimulate the formation of macrophage colonies. Hence, the ability of alveolar macrophages to clear the surfactant is affected in PAP. As a result of these alterations, there is accumulation of the surfactant in the alveoli along with respiratory problems and increased infections due to PAP. Furthermore, this disease may secondarily cause cancer, hematological diseases, and toxic inhalation.

Pulmonary alveolar proteinosis has also been associated with immune deficiencies, such as agammaglobulinemia, combined immunodeficiency, and organ transplantation. Moreover, hematological disorders, including acute myeloid leukemia, myeleodysplastic syndromes, acute lymphoid leukemia, lymphoma, and myeloma can also cause PAP. Patients may be neutropenic secondary to chemotherapy, and infectious pathogens may be isolated from the BALF. Additionally, respiratory insufficiency and fever can be observed in PAP patients, and lung cancer may also may be associated with this disease.[27]

In our Turkish cases, one had immune deficiency (agammaglobulinemia) and another had a hemotological disorder (acute lymphocytic leukemia precursor B cell type). The first was diagnosed at the age of eight via an open lung biopsy. The patient was hospitalized three times, and WLL was performed. She was reported to be alive three years after the diagnosis and asymptomatic.[7] Febril neutropenia was reported in the second case after the 38th day of chemotherapy. After receiving antibiotics and GM-CSF, the lesions were no longer visible on high-resolution computed tomography (HRCT), but the patient died a year later from a relapse of acute lymphoblastic leukemia (ALL).[8]

Pulmonary alveolar proteinosis may also be connected with the inhalation of mineral, metal, or organic particles. In French and Japanese studies, 23-39% of PAP patients reported exposure to these types of particles.[27] In this study, we found six cases (25%) of toxic particle inhalation, one of which was attributed to asbestos, two to welding smoke, and three to agricultural particles.

Surfactant mutations and genetic defects in the GM-CSF receptor along with lysinuric protein intolerance can cause the genetic PAP subtype.

In addition, the homozygous frame shift mutation in the porcine surfactant protein B (SFTPB) gene can cause congenital PAP, and altered distribution of the SFTPA gene has been observed in lung specimens.[28] We confirmed SP-B deficiency in one of cases after an autopsy, and the brother of this patient who had died a year earlier had also been diagnosed with PAP.[6]

Signs-Physical examination

Pulmonary alveolar proteinosis usually presents with dyspnea, cough, weight loss, chest pain, hemopthysis, and malaise. Fever and hemopthysis can be signs of accompanying infection. A physical examination is often normal, but crackles may be observed at the lung bases along with cyanosis and clubbing.[29] In the Turkish cases that we examined, the symptoms were reported as follows: dyspnea

(96%), cough (71%), fever (38%), sputum (21%), chest pain (13%), weight loss (13%), leg swelling (8%), and hemopthysis (4%). Six cases had received antibiotics during their hospitalization. In four of the cases (17%), normal physical findings were reported, but there were fourteen cases (58%) of crackles at the lung bases, 12 (50%) of cyanosis, four (17%) of clubbing, four (17%) of subcostal retractions, two (8%) of lower extremity edema, and one (4%) of hepatosplenomegaly.

Radiology

Conducting a chest X-ray is the first step toward diagnosing PAP, but it demonstrates nonspecific signs. However, ground glass and reticulonodular opacities that are symmetrical and perihilar in nature along with consolidations with air bronchograms and diffuse bilateral infiltrations in all lung fields can be observed via this method. Chest X-rays can also reveal apical lung fields and costophrenic sinuses that have been preserved. The radiological appearance of PAP resembles pulmonary interstitial edema without pleural effusion and cardiomegaly. In addition, pleural effusion, lymphadenopathy, and cavitary lesions can be observed in accompanying pulmonary infections.[29] In this study, we found that in 23 cases who underwent chest X-rays, 11 (48%) had diffuse consolidations, nine (39%) had perihilar consolidations, and three (13%) had dominant consolidations in the lower lung zone.

Computed tomography is better for revealing the anatomy and showing the extension of PAP disease. Crazy-paving appearance refers to the ground glass opacity with septal thickening. This sign is generally bilateral and diffuse with the unaffected lung fields identified by sharp borders. On CT, crazy paving can be diffuse or regional as well as symmetrical or asymmetrical. Sixteen cases in this study had chest CT results. Nine (56%) had crazy paving, five (31%) had ground glass opacity, and two (13%) had superposition of infection pattern. Lung function capacity is related to the extent of ground glass appearance and consolidation. Although crazy paving is typical in PAP, it can also be observed in various infectious, hemorrhagic, or neoplastic conditions, including left ventricular insufficiency, pneumonia, alveolar hemorrhage, bronchoalveolar carcinoma, and diffuse alveolar injury.

Diagnosis

The milky appearance in the BALF is typical for PAP, and an examination showed of this fluid showed PAS-positive fields in the alveoli. Furthermore, foamy macrophages can be observed microscopically. Lamellar bodies on electron microscopy can also confirm the diagnosis of PAP. When unsatisfactory BALF is obtained, transbronchial or open lung biopsies are sometimes performed.[29]

In this retrospective study, BALF was obtained in 14 cases (58%) while 10 (42%) underwent an open lung biopsy. Additionally, transbronchial biopsies were performed on nine cases (38%), and electron microscopy confirmation was needed in four others. (17%). Three cases (13%) were also diagnosed after an autopsy.

Hypoxia is due to alveolar depositions which affect the transport of oxygen from the alveoli. High levels of LDH have also been reported as a disease severity marker.[30,31]

Sixteen of our cases reported the presence of LDH. Ten (63%) of these had elevated LDH levels while six were within the normal range.

Spirometry reveals a restrictive pattern when hypoxemia and reduced DLCO are observed in PAP cases.[27] Of the 13 cases that we evaluated who had spirometry results, two (15%) reported normal findings while four (31%) had mild, three (23%) had moderate, and four (31%) had severe reduction. Only six of the cases had DLCO test results. Mild reduction was reported in one case, with moderate reduction in two others, and severe reduction in the other three.

Serum surfactant protein SP-A, SP-B and SP-D levels are increased in PAP.[9] One of the Turkish cases had SP-A expression in a histological specimen and was diagnosed with PAP after an autopsy.

Elevated concentrations of iron, transferrin, transferrin receptor, lactoferrin, and ferritin have been observed in the alveolar space in recent studies.[28] In our study, the baby boy who was diagnosed with PAP via an autopsy also had liver hemosderosis and extramedullary hematopoiesis, and his brother, who was born a year later and died 30 minutes after being born, was also diagnosed with genetic PAP.[6]

Treatment

Although spontaneous remission is observed in some patients, WLL is the recognized standard of care for PAP patients with respiratory symptoms.[29] After general anesthesia and double lumen intubation, large amounts of warmed sterile saline in 1-2 liter doses for a total of up to 15 to 60 liters are administered through the tube to one lung while single lung ventilation is performed on the other side. By mechanical washing of the lung with saline and percussion to the chest, the excess amount of material from the alveoli, which is composed of surfactant, is removed. When the BALF

becomes clear, the procedure is ended. However, it may be necessary for the contralateral lung to be lavaged one or two days later. In addition, WLL can be performed at various times when indicated, but it must be performed once only one lung at a time.

Thirteen of the cases (54%) in our study received nonspecific treatments, for example antibiotics, steroids, or oxygen support, or they were merely observed. Whole lung lavage was eventually performed in six of these cases (25%), and segmental lung lavage in four others (17%). Additionally, one of the cases (4%) was treated with IVIG while GM-CSF was used in another (4%).

Therapy with GM-CSF is another treatment choice via either inhalation or the subcutaneous route. In the study by Borie et al.,[27] improvement was observed with this type of treatment in PAP patients (48% to 68%) when used in the autoimmune subtype. Therefore, GM-CSF is considered to be an alternative choice to WLL. The case who received GM-CSF in our study also had a hematological malignancy. In a study by Şimşek et al.,[10] HRCT revealed that the infiltrations disappeared after this treatment option. The case who received IVIG therapy had agammaglobulinemia, and WLL was also performed along with the use of GM-CSF. The hypoxia then improved, and the lung infiltrations diminished afterwards.[7]

Prognosis

Spontaneous remission can be observed in the autoimmune subtype of PAP, as was seen in 10 of 15 asymptomatic untreated patients in a French cohort and 11 of 39 patients in a Japanese cohort.[32,33] Whole lung lavage therapy and GM-CSF may be beneficial, but some patients do not respond to any type of therapy. However, the five-year survival rate for autoimmune PAP with WLL is nearly 95%.[27]

Five of the cases in our study died during hospitalization, but four with a hypoxic condition improved and were discharged from the hospital. Furthermore, three cases showed improved lung function tests, and five had regression of the lesions on chest X-ray. Thirteen of the cases who were discharged from hospital were reported to be under follow-up periods ranging from three months to four years.

Limitations

The cases that we reported in this study were all full text articles. During the study period, we also found some cases on internet search engines that had been reported in national congresses as thematic poster sessions. Since these may have been in congresses held by different specialties, it was not possible to find all of these cases nor could we always contact the presenters. Information presented in poster sessions is often limited, thus these PAP cases may not have been reported in journals. Moreover, we believe that PAP disease is underdiagnosed in Turkey as there are a relatively small number of reported cases for a country that has a population of approximately 74 million.

In conclusion, 24 Turkish PAP cases were reviewed in this study. Dyspnea, cough, and fever were the most reported symptoms, and crackles at the lung bases and cyanosis were the most common physical findings. Chest X-rays and CT were used as the preferred imaging techniques in these cases, and different types of diagnostic procedures (EM, BALF, TBB, OLB) and therapies (WLL, BAL, IVIG, GM-CSF) were applied that corresponded to the those used in the published data. Five cases died during hospitalization, four reported improved hypoxia, three had improved lung function test results, and five had regression of the lesions on chest X-ray. Interestingly, seven of the adult PAP cases had previously received antituberculous treatment, which might because of the high prevalence of tuberculosis (TB) in Turkey. Some of the PAP patients did not respond to antibiotic therapy, which was surprising since the imaging findings indicated that this treatment was necessary. For this reason, in some cases, invasive procedures might have to be performed to diagnosis PAP.

Declaration of conflicting interests

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REFERENCES

1. Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med 2002;166:215-35.
2. Trapnell BC, Carey BC, Uchida K, Suzuki T. Pulmonary alveolar proteinosis, a primary immunodeficiency of impaired GM-CSF stimulation of macrophages. Curr Opin Immunol 2009;21:514-21. doi: 10.1016/j.coi.2009.09.004.
3. Goerpe A, Kuyumcuyan K, Ercan H, Ozkan E. Pulmonary alveolar proteinosis. (apropos of 2 cases). [Article in Turkish] Tip Fak Mecm 1964;27:72-9.
4. Hızarcıoğlu M, Kayserili E, Ecevit Ç, Gülez P, Apa H, Ortaç R. Pulmoner alveolar proteinozisli bir olgu. Pulmonary alveolar proteinosis: a case report. Ege Ped Bül 2003;10:151-4.
5. Doğru D, Yalçin E, Aslan AT, Ocal T, Ozçelik U, Güçer S,

et al. Successful unilateral partial lung lavage in a child with pulmonary alveolar proteinosis. J Clin Anesth 2009;21:127-30. doi: 10.1016/j.jclinane.2008.06.035.
6. Meşe T, Dizdarer C, Aktaş S, Özcan T, Ülker Ü. Konjenital pulmoner alveoler proteinozis (İki kardeşte olgu sunumu). Türkiye Ekopatoloji Dergisi 2003;9:81-4.
7. Patiroglu T, Akyildiz B, Patiroglu TE, Gulmez IY. Recurrent pulmonary alveolar proteinosis secondary to agammaglobulinemia. Pediatr Pulmonol 2008;43:710-3. doi: 10.1002/ppul.20818.
8. Pamuk GE, Turgut B, Vural O, Demir M, Hatipoğlu O, Unlü E, et al. Pulmonary alveolar proteinosis in a patient with acute lymphoid leukemia regression after G-CSF therapy. Leuk Lymphoma 2003;44:871-4.
9. Özdemir N, Ardıç S, Tel T, Ekici M, Metintaş M, Çerezci V ve ark. Parankim fibrozisinin eşlik ettiği pulmoner alveoler proteinozis. Solunum Hastalıkları 1991;2:55-60.
10. Şimşek C, Kalaycıoğlu O, Beder S, Tunç M, Evirgen O, Ertürk Ş. Kaynakçı siderozisi ve pulmoner alveoler proteinozis (bir olgu sunusu). Turkiye Klinikleri J Med Sci 1992;12:250-3.
11. Baran R, Aksoy F, Ertan FÜ, Özyaran K, Tor M. Pulmoner alveoler proteinozis balgam incelemesi ve segmental lavaj ile tanı. Pulmonary alveolar proteinosis: diagnosis by sputum examination and segmental lavage. Solunum 1994;19:688-92.
12. Köktürk N, Oğuzülgen İK, Türktaş H, Ahmet Mahli A. A case report: Pulmonary alveolar proteinosis. Turkish Respiratory Journal 2000;1:68-72.
13. Kaçar N, Ünsal Ş, Çakan A, Tuksavul F, Ermete S, Güçlü SZ. Pulmoner alveoler proteinozis (Olgu sunumu). Tüberküloz ve Toraks Dergisi 2000;48:162-6.
14. Çiftçi TU, Şipit T, Apaydın Z, Çoban G, Oğuz D. Pulmoner alveoler proteinozis (PAP) (Bir olgu nedeniyle). Solunum Hastalıkları 2001;12:71-4.
15. Seyfikli Z, Gönlüuğur U, Berk S, Arıcı S, Kap M. Primary alveolar proteinosis and review of the literature. Turkish Respiratory Journal 2001;2:36-9.
16. Gülsüm M, Arıyürek M, Başaran Demirkazık F, Fırat P. Yüksek rezolüsyonlu bilgisayarlı tomografide Arnavut kaldırımı görünümü oluşturan bronşioloalveoler kanser ve pulmoner alveoler proteinozis: İki olgu sunumu. Bilgisayarlı Tomografi Bülteni 2002;7:38-40.
17. Polat G, Yılmaz U, Yalnız E, Ermete S, Utkaner G. Pulmoner alveoler proteinozis (olgu sunumu). İzmir Göğüs Hastanesi Dergisi 2003;17:73-7.
18. Sazak HG, Göktaş U, Alagöz A, Gülhan M, Şahan L, Şavkılıoğlu E ve ark. Pulmoner alveoler proteinozis uygulanan masif bronkoalveoler lavajda anestezi (olgu sunumu). GKD Anest Yoğ Bak Dern Derg 2003;9:77-81.
19. Sancak S, Karakurt S, Ceyhan B, Çelikel T. Bronkoalveoler lavaj sonrası ARDS gelişen pulmoner alveoler proteinozisli hasta. Yoğun Bakım Dergisi 2004;4:195-9.
20. Gavaf M, Karasu I, Çakan A, Özsöz A, Aydoğdu Z. Pulmoner alveoler proteinozis (olgu sunumu). İzmir Göğüs Hastanesi Dergisi 2007;21:41-6.
21. Edis EC, Tabakoglu E, Caglar T, Hatipoglu ON, Cevirme L, Alagol A. Treatment of a primary pulmonary alveolar proteinosis case with severe hypoxaemia by using segmental lavage technique. Ann Acad Med Singapore 2007;36:871-2.
22. Uyar M, Elbek O, Çiftçi N, Şanlı M, Bakır K, Dikensoy Ö. Fatal seyirli pulmoner alveoler proteinozis. Tur Toraks Der 2008;9:177-80.
23. Tutar N, Gülmez İ, Hasdıraz L, Büyükoğlan H, Demir R, Oymak FS ve ark. Pulmoner alveoler proteinozis (vaka sunumu). Solunum 2009;11:43-5.
24. Yildiz T, Ates G, Bogatekin G, Ozmen CA, Mizrak B. A case of idiopathic pulmonary alveolar proteinosis. Respiratory Medicine CME 2010;3:267-9.
25. Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. N Engl J Med 1958;258:1123-42.
26. Kitamura T, Tanaka N, Watanabe J, Uchida, Kanegasaki S, Yamada Y, et al. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med 1999;190:875-80.
27. Borie R, Danel C, Debray MP, Taille C, Dombret MC, Aubier M, et al. Pulmonary alveolar proteinosis. Eur Respir Rev 2011;20:98-107. doi: 10.1183/09059180.00001311.
28. Huizar I, Kavuru MS. Alveolar proteinosis syndrome: pathogenesis, diagnosis, and management. Curr Opin Pulm Med 2009;15:491-8. doi: 10.1097/MCP.0b013e32832ea51c.
29. Vancheeswaren R, Morgan C, Wells AU. Pulmonary alveolar proteinosis. Investigation and management- a review. Clin Pulm Med 2007;14:360-4.
30. Hoffman RM, Rogers RM. Serum and lavage lactate dehydrogenase isoenzymes in pulmonary alveolar proteinosis. Am Rev Respir Dis 1991;143:42-6.
31. Seymour JF, Doyle IR, Nakata K, Presneill JJ, Schoch OD, Hamano E, et al Thorax. Relationship of anti-GM-CSF antibody concentration, surfactant protein A and B levels, and serum LDH to pulmonary parameters and response to GM-CSF therapy in patients with idiopathic alveolar proteinosis. Thorax 2003;58:252-7.
32. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med 2008;177:752-62. doi: 10.1164/rccm.200708-1271OC.
33. Briens E, Delaval P, Mairesse MP, Valeyre D, Wallaert B, Lazor R, et al. Pulmonary alveolar proteinosis. Rev Mal Respir 2002;19:166-82.