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CASE REPORT
OLGU SUNUMU

The investigated case of etiology of chylous pleural effusion: Ataxia-telangiectasia

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ABSTRACT

The investigated case of etiology of chylous pleural effusion: Ataxia-telangiectasia

Ataxia-telangiectasia is an autosomal recessive, rare, neurodegenerative multisystem disorder characterized by ataxia-telangiectasia, cerebellar ataxia, oculocutaneous telangiectasia, immunodeficiency, progressive respiratory failure associated with increased malignancy risk. Clinical diagnosis is made with ataxia-telangiectasia mutated (ATM) gene. Our case, who was diagnosed as ataxia-telangiectasia while investigating the etiology of chylous pleural effusion, is presented because of its rare occurrence.

Key words: *Ataxia-telangiectasia; malignancy; immunodeficiency; chylous effusion*

ÖZ

Şilöz plevral effüzyon etiyolojisi araştırılan olgu: Ataksi-telenjiektazi

Artmış malignite riski ile ilişkili olan ataksi-telenjiektazi, serebellar ataksi, okülokütanöz telenjiektazi, immün yetmezlik, ilerleyici solunum yetmezliği ile karakterize, otozomal resesif, nadir, nörodejeneratif multisistem bir hastalıktır. Ataksi-telenjiektazide mutasyona uğramış (ATM; Ataxia Telangiectasia Mutated) genin gösterilmesi ile klinik tanı doğrulanır. Şilöz plevral effüzyon etiyolojisi araştırılırken ataksitelenjiektazi tanısı alan olgu, nadir görülmesi nedeniyle sunulmuştur.

Anahtar kelimeler: *Ataksi-telenjiektazi; malignite; immün yetmezlik; şilöz effüzyon*

INTRODUCTION

Ataxia-telangiectasia is an autosomal recessive multisystem disease characterized by DNA repair disorder, cerebellar dysfunction, susceptibility to malignancies, sensitivity to ionizing radiation, and immune system disorders (1,2).

The patient, followed up with the diagnosis of ataxic cerebral palsy, is noteworthy because she was diagnosed with ataxia-tel-

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angiectasia while investigating the etiology of chylous pleural effusion in our clinic, and gastrointestinal system malignancy was detected in about the increased malignancy risk.

CASE REPORT

A 24-year-old female patient followed up with cerebral palsy was admitted to the emergency department because of dyspnea. Growth-development retardation, speech disorder, and immobilization were observed in the patient. Physical examination revealed lymphadenopathy (LAP) in the bilateral cervical and inguinal region and respiratory system auscultation revealed decreased respiratory sounds in the bilateral lower zone. In posteroanterior (PA) chest X-ray, bilateral pleural effusion was observed (Figure 1).

Laboratory values were hemoglobin 7.3 g/dL, lymphocyte 930/μL and CRP 6.5 mg/dL, creatinine 1.96 mg/dL, D-Dimer 864 ng/mL. Diagnostic thoracentesis with left hemithorax revealed a chylous pleural effusion, a triglyceride level of 555 mg/dL, and a pleural catheter was inserted because of effusion with a chylous character (Figure 2).

Acinetobacter baumanii growth was detected in the pleural fluid culture, antibiotic therapy was arranged. In the follow-up, when the previous records of the patient were examined, in the cranial magnetic resonance imaging dated 2014; significant atrophy findings were detected in both cerebellar hemispheres, cerebellar peduncle, and vermis. Therefore, it was recommended to investigate in terms of familial cerebellar aplasia/atrophy types. The patient, who was followed up with the diagnosis of cerebral palsy, did not have any limitation in motor skills until the age of eight years, but later had progressive muscle weakness, loss of balance, and a history of frequent recurrent infections after which was consulted to neurology and ophthalmology with the preliminary diagnosis of ataxia-telangiectasia. The patient's electromyography was compatible with severe sensorimotor polyneuropathy. In her ophthalmological examination, telangiectatic vessel appearances were found in the right nasal and left temporal. AFP and CA-19-9, CA-15-3, CA-125 tumor markers requested for the diagnosis of ataxia-telangiectasia in the patient; AFP 140 ng/mL, CA-125 327 U/mL, CA-19-9 18441 U/mL was detected. Grade 1 hydronephrosis on the right and Grade 2 hydronephrosis on the left, free fluid in the pelvic region, paracolic, peri hepatic area, and

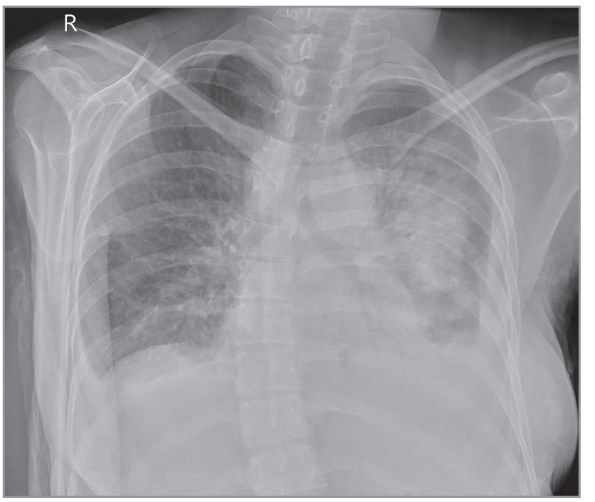

Figure 1. PA chest X-ray shows bilateral pleural effusion, which is more prominent in the left costophrenic sinus, enlargement in the upper mediastinum and irregularly bordered opacity in the left middle zone.

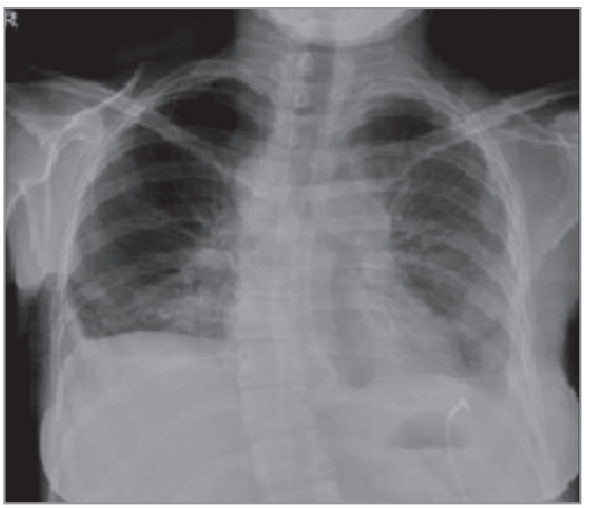

Figure 2. After drainage with left pleural catheter, regression is observed in left pleural effusion in PA chest X-ray.

significant contrast enhancement in the gastric mucosa were observed in abdominal computed tomography (CT) (Figure 3).

Multiple pathological lymph nodes were detected in the neck and superficial tissue ultrasonography performed to investigate the patient's lymphoma, gastrointestinal system malignancy, and gynecological malignancy. Excisional biopsy pathology applied to the left inguinal lymphadenopathy primarily reported as signet ring cell carcinoma metastasis that may originate from the gastrointestinal tract. There was no finding in favor of malignancy in pleural fluid cytolo-

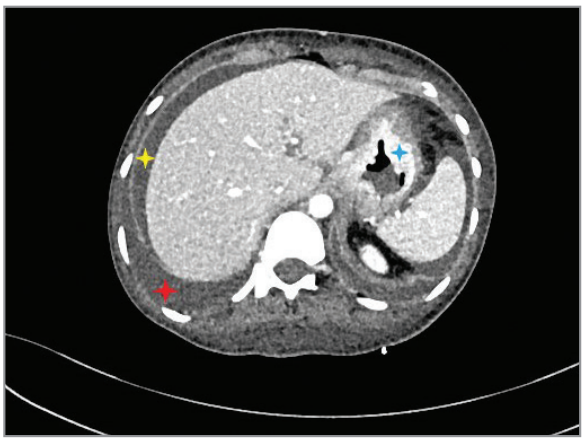

Figure 3. Abdominal CT section shows free fluid in the abdomen by red mark , pleural fluid by yellow mark and contrast enhancement in the gastric mucosa by blue mark.

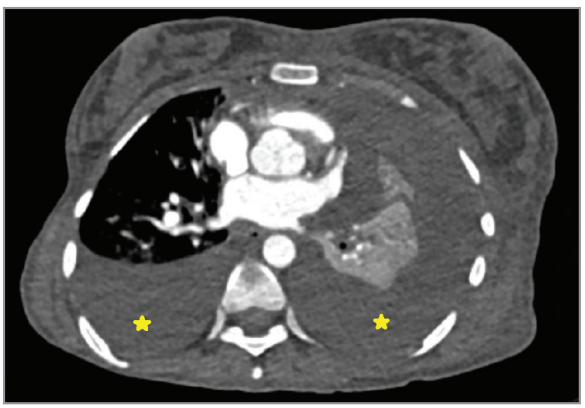

Figure 4. Thorax CT section shows bilateral pleural effusion by yellow mark.

gy. For the evaluation of immunodeficiency, IgA level 25 mg/dL, IgG 884 mg/dL, IgM 105 mg/dL was detected. Hepatitis markers and HIV RNA were negative. Genetic mutations specified in the patient's gene were heterozygous. Thus, a diagnosis of ataxia-telangiectasia was made with the current laboratory, clinical and genetic mutation results. Progression in creatinine values, electrolyte disturbance, and hypotension were observed in the follow-up. Cardiac arrest developed, and she was intubated after cardiopulmonary resuscitation and was taken under intensive care follow-up and died. The patient's endo colonoscopy, which was planned to screen for malignancy in the gastrointestinal tract, could not be performed. The family was called for genetic counseling, but the relatives of the patients reported they could not come because of socioeconomic reasons.

DISCUSSION

Chylous pleural effusion is characterized by a milky appearance, >110 mg/dL pleural triglyceride level, or chylomicrons in 50% of cases (3,4). Hematologic and solid tumors such as lymphoma, lung cancer, myeloma, mediastinal Kaposi's sarcoma may cause chylous pleural effusion (4). In our case, gastrointestinal tract mucinous adenocarcinoma was considered as the cause of chylous effusion, but the etiology of chylous effusion could not be clarified since the pleural effusion cytology was reported as benign and could not be repeated afterward. The pleural fluid had a milky appearance and was evaluated as chylous fluid because triglyceride level was 555 mg/dL.

Ataxia-telangiectasia (AT), also known as Louis-Bar Syndrome, is an autosomal recessive disease characterized by cerebellar degeneration, telangiectasia, immunodeficiency, susceptibility to cancer, and radiation sensitivity. There is an equal influence in all ethnicities except relative populations; its worldwide prevalence is estimated to be 1/40000-1/100000 (5,6). ATM deficiency is the second most common cause of monogenic primary immunodeficiency after familial Mediterranean fever (6).

ATM gene is on the human chromosome 11q22-q23. ATM protein provides coordination of cell signaling pathways in response to DNA double-strand breaks, oxidative stress, and other genotoxic stress, and manages apoptosis. Because of ATM deficiency, an increase in the expression of hypoxia-induced factor-1, VEGF is observed; ,it plays a role in vascular abnormalities such as cardiovascular diseases, telangiectasia, and tumor development (6).

Kinase activity level and residual protein function are determinants of the disease phenotype (2). Because of missense and frameshift mutations, functional ATM protein production and kinase activity may occur; disease severity is less, and progression is slow; patients are referred to as atypical, late-onset, or variant. More severe forms are called classic, typical, or early onset (1). Our case was in the classical ataxia-telangiectasia phenotype despite carrying a heterozygous mutation.

Cerebellar symptoms (67%), dystonia (18%), choreoathetosis (10%), and tremor (4%) are present in the initial findings of ataxia-telangiectasia. Other prominent findings are oculomotor apraxia, cutaneous or

conjunctival telangiectasia, nystagmus, dysarthria, neuropathy, immunodeficiency, high serum alpha-fetoprotein (AFP) level (2). Our case had conjunctival telangiectasia, immunodeficiency, ataxia, neuropathy, and elevated serum AFP.

Ocular telangiectasia often occurs at 5-8 years, sometimes it may not be seen at all. The absence of telangiectasia does not exclude the diagnosis of AT (1). In the ophthalmologic examination of our case, telangiectatic vessel appearances were found in the nasal right on the right and the temporal on the left.

About two-thirds of the people with AT have immune system abnormalities; most patients have low levels of IgA, dL, IgG or their subclasses, inability to produce adequate antibodies against vaccines or infections, total and naive CD4 T cell deficiency, and lymphopenia. Elevated IgM levels can be observed in 10% of patients with classical AT; It should warn about the HIGM phenotype and the development of lymphoma. In our case, lymphopenia and IgA were low, and IgM and IgG levels were normal.

Recurrent bacterial sinopulmonary infections because of immunological disorders, progressive dysphagia, and aspiration in ataxia-telangiectasia are observed in over 25% of patients. Our case had a history of recurrent infections since childhood; in the follow-up, *A. baumanii* growth was observed in the pleural fluid culture.

Inflammation, oxidative stress, and failure to repair lung damage are associated with both idiopathic and genetic-based interstitial lung disease (ILD). It should be noted that pulmonary involvement of lymphoma can also mimic ILD.

Decreased physical fitness can lead to decreased respiratory tidal volume, restrictive dysfunction, and low functional vital capacity (FVC) (1).

People with ataxia-telangiectasia have a lifetime risk of developing malignancy of 10-38% (1,5,6). Patients are susceptible to both lymphoid and solid tumors (3,4,6). AT patients are at a 70-to 200-fold increased risk of developing hematological malignancies (70–80% of all neoplasms) compared to the general population (8). Nearly all hematologic malignancies can develop pleural effusions during the clinical course of disease (9).

Low IGA levels are reported as a biomarker for the development of lymphoid cancer. Compared to other non-carrier family members, the risk of breast cancer 5.1, gastric cancer 1.5, pancreatic cancer 2.2, colorectal cancer 1.3, bladder cancer 2.4, and melanoma 2.1 times increased in ATM heterozygous mutation carriers (7). In our case, gastrointestinal system mucinous adenocarcinoma was considered.

Growth disturbances are found in approximately 75% of children with ataxia-telangiectasia; malnutrition and abnormal IGF-1 (insulin-like growth factor-1) secretion are held responsible (1,5). Our patient had growth-development retardation and malnutrition.

The reason for the high AFP level in ataxia-telangiectasia is unknown, 95% of the patients have high serum AFP levels after the age of two (1,2,5). Serum AFP level of our case was 140 ng/mL.

Differential diagnosis is possible with clinical features and selected laboratory tests (3,6). For definitive diagnosis, DNA sequencing, western blot, or kinase assays to detect abnormal protein levels/activity can be used (5).

Children with classical ataxia-telangiectasia walk at a normal age, but can not develop further (1). Since most children with classical AT have stable neurological symptoms in the first 4-5 years of their lives, they may be misdiagnosed as “ataxic cerebral palsy” (1); our case was followed up with the diagnosis of ataxic cerebral palsy before.

Patients with ataxia-telangiectasia have a poor prognosis and a median life expectancy of 25 years (2).

There are very few studies showing the association of ataxia-telangiectasia and pleural effusion (9,10). However, in all of these studies, pleural effusion has been found secondary to the malignancy accompanying ataxia-telangiectasia. Ozyoruk et al. have described chylous pleural effusion in a case of childhood ataxia-telangiectasia and T-cell acute lymphoblastic lymphoma (10). The case presented in this study is similar to the case we presented because of its pleural fluid with chylous character. However, chylous pleural effusion has been associated with mediastinal mass compression and damage to the thoracic duct. In our case, chylous pleural effusion was not associated with malignancy and did not recur at follow up.

CONCLUSION

Ataxia-telangiectasia should be considered in patients with a history of ataxia, and differential diagnosis should be made from other diseases progressing with ataxia, especially such as cerebral palsy. Genetic examination should be requested from patients, families should be directed to antenatal diagnosis, and patients should be followed up with a multidisciplinary approach because of multiple comorbidities.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: ZY, YH, DK

Analysis/Interpretation: PÇ, YH, IS

Data Acquisition: IS, ZY, DK

Writing: DK, PÇ, IS

Critical Revision: YH, IS, DK

Final Approval: PÇ, IS

REFERENCES

1. *Song P, Zhang J, Shang C, Zhang L. Refractory chylous pleural effusion with systemic lupus erythematosus. Z Rheumatol 2019; 78(8): 797-802. https://doi.org/10.1007/s00393-018-0545-z*
2. *Riley L, Ataya A. Clinical approach and review of causes of a chylothorax. Resp Med 2019; 157: 7-13. https://doi.org/10.1016/j.rmed.2019.08.014*
3. *Oviatt C, Wright J, Greift M, McGrath-Morrow S, Crawford T, Lederman H. Ataxia-telangiectasia: a review. Orphanet J Rare Dis 2016; 11: 159. https://doi.org/10.1186/s13023-016-0543-7*
4. *Os N, Haaxma C, Flier M, Merkus P, Deuren M, Groot I, et al. Ataxia-telangiectasia: recommendations for multidisciplinary treatment. Dev Med Child Neurol 2017; 59(7): 680-9. https://doi.org/10.1111/dmcn.13424*
5. *Levy A, Lang A. Ataxia-telangiectasia: a review of movement disorders, clinical features, and genotype correlations. Movement Disorders 2018; 33(8): 1238-47. https://doi.org/10.1002/mds.27319*
6. *Amirifar P, Ranjouri M, Yazdani R, Abolhassani H, Aghamohammadi A. Ataxia-telangiectasia: a review of clinical features and molecular pathology. Pediatr Allergy Immunol 2019; 30(3): 277-88. https://doi.org/10.1111/pai.13020*
7. *Os N, Roeleveld N, Weemaes C, Jongmans M, Janssens G, Taylor A, et al. Health risks for ataxia-telangiectasia mutated heterozygotes: a systematic review, meta-analysis and evidence-based guideline. Clinical Genetics 2016; 90(2): 105-17. https://doi.org/10.1111/cge.12710*
8. *Sharma L, Kashyap R, Gupta S, Bhargava M. B-Cell acute lymphoblastic leukemia in a child with ataxia-telangiectasia. Pediatr Hematol Oncol 2008; 25: 473-76. https://doi.org/10.1080/08880010802106614*
9. *Keklik M, Koker M, Sivgin S, Camlica D, Pala C, Çetin M, et al. detection of acute lymphoblastic leukemia involvement in pleural fluid in an adult patient with ataxia telangiectasia by flow cytometry method. Indian J Hematol Blood Transfus 2014; 30: 73-6. https://doi.org/10.1007/s12288-013-0253-4*
10. *Ozyoruk D, Guzelkucuk Z, Hacisalihoglu S, Cinel G. The development of chylothorax in a child with t-cell lymphoblastic lymphoma and ataxia telangiectasia during induction therapy. J Pediatr Hematol Oncol 2020; Publish Ahead of Print. https://doi.org/10.1097/MPH.0000000000002039*