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HOW REAL IS THE DIAGNOSIS OF COPD IN A YOUNG PATIENT?

Sorin Bivolaru[1], Ancuța Constantin[2], Monica Marinescu[3]
[1]Doctoral School, University of Medicine and Pharmacy "Carol Davila" Bucharest
[2]University of Medicine and Pharmacy "Carol Davila" Bucharest - Faculty of Medicine and Pharmacy
[3]Doctoral School, "Lower Danube" University of Medicine and Pharmacy, Galați
Corresponding author: Sorin Bivolaru
E-mail: sorinbivolaru@yahoo.com

Abstract

We present the case of a young patient, known to have COPD and DZ, who presented to the emergency room for dyspnea and sudden onset right laterobasal pain. From the patient's recent history we note episode of right total pneumothorax five days prior to presentation to our unit, for which pleural drainage was fitted. Clinical examination and standard chest X-ray performed in the emergency department established the diagnosis of recurrent total pneumothorax. Given the medical history and recent history of pneumothorax in a young heavy smoker patient with two episodes of right pneumothorax, one of which was recent, known with diabetes mellitus and COPD, with imaging changes such as "reticulo-nodular lesions with cystic appearance and interstitial fibrosis on the left lung area", the diagnosis of COPD was questioned and the suspicion of pulmonary histiocytosis X was raised, which is why, together with the radiologist and thoracic surgeon, the decision was made to perform a surgical treatment and a lung biopsy to establish a definite diagnosis. The result of the lung biopsy confirmed the suspicion of pulmonary histiocytosis X.

Since in histiocytosis X the damage is multi-organ, one month postoperatively the patient underwent a complex biological, functional and imaging evaluation to identify or exclude other affected organs. Imaging and functional investigations performed, collaborated with the patient's history, age and medical history refuted the diagnosis of COPD. Therapeutically for pulmonary histiocytosis X it was recommended to stop smoking urgently and monitor respiratory function at 6 months in the first year after diagnosis.

Keywords: *COPD, smoking, histiocytosis, diabetes mellitus, clinical case, pneumothorax.*



Internal Medicine

Clinical Cases

Rezumat

Prezentăm cazul unui pacient tânăr, cunoscut cu bronhopneumopatie cronică obstructivă (BPOC) și diabet zaharat (DZ), care s-a prezentat la serviciul de urgență pentru dispnee și durere laterobazală dreaptă cu debut brusc. Din istoricul recent al pacientului remarcăm episod de pneumotorax drept cu cinci zile înainte de prezentarea la unitatea noastră, pentru care s-a practicat drenaj pleural.

Examenul clinic și radiografia toracică standard efectuată în serviul de urgență au stabilit diagnosticul de pneumotorax total recidivant. Având în vedere istoricul medical și antecedentele recente de pneumotorax la un tânăr cunoscut cu diabet zaharat și BPOC, mare fumător, cu două episoade de pneumotorax drept, dintre care unul recent, cu modificări imagistice precum „leziuni reticulo-nodulare cu aspect chistic și fibroză interstițială la nivelul plămânului stâng", diagnosticul de BPOC a fost pus la îndoială și s-a ridicat suspiciunea de histiocitoză X. Împreună cu radiologul și chirurgul toracic, s-a luat decizia de a efectua tratament chirurgical și de a preleva o biopsie pulmonară pentru stabilirea diagnosticului de certitudine. Rezultatul biopsiei pulmonare a confirmat suspiciunea de histiocitoză pulmonară X.

Întrucât în histiocitoza X afectarea este multiorganică, la o lună postoperator pacientul a fost supus unei evaluări biologice, funcționale și imagistice complexe pentru identificarea sau excluderea altor organe afectate. Investigațiile imagistice și funcționale efectuate, în coroborare cu istoricul pacientului, vârsta și istoricul medical au infirmat diagnosticul de BPOC. În scop terapeutic, pentru histiocitoza pulmonară X, s-a recomandat renunțarea de urgență la fumat și monitorizarea funcției respiratorii la 6 luni în primul an de la diagnostic.

Cuvinte cheie: *BPOC, fumat, histiocitoză, diabet zaharat, caz clinic, pneumotorax.*

We present the case of a 33-year-old young man, smoker 25 PA, known with COPD and DZ, who presented to our emergency department for dyspnea and sudden onset right latero-basal pain in the absence of sustained physical exertion - driver. Clinical examination in the emergency room finds a patient: obese, conscious, cooperative, BP 145/88 mmHg, AV - 112/minute, rhythmic, FR - 24/minute, SpO2 90% without resting O2. Pulmonary - absent vesicular murmur on the right lung area. Vesicular murmur present without rales on the left lung area. M - 174, G - 120 kg (BMI - 39.64). Usual blood tests performed in the emergency room within normal limits. On standard chest X-ray (radiological image unavailable) - hypertransparency and absence of lung pattern over the entire right lung area. Reticulo-nodular lesions with cystic appearance and interstitial fibrosis on the left lung area.

Medical history

From the patient's recent medical history we note: 120 hours (5 days) prior to presenting to our unit, he presented to an emergency room outside Romania for sudden onset dyspnea - patient at rest. Investigations established the diagnosis of right total pneumothorax for which pleural tube drainage was fitted in the first 24 hours after presentation and clinically and imaging monitored for another 48 hours after removal of the drainage tube. Forty hours after discharge, being a driver, dyspnea and right laterothoracic pain with junctional character suddenly recurred. For this symptomatology, the patient was given painkillers as recommended at discharge. Under pain relief treatment, the pain improved considerably, but the dyspnea worsened, which is why 8 hours later the patient presented to the emergency room of our unit. Also from the patient's anamnesis we note: history of spontaneous right pneumothorax drained on tube 5 years before presenting to our unit (age 28 years), Diabetes mellitus type II diagnosed at the age of 19 years under treatment with Siofor and Ozenpic, COPD risk group B diagnosed at the age of 31 years under treatment with Spiolto Respimat, single congenital right kidney, Gout under treatment with Milurit 300 mg and Obesity grade II.

Given the medical history and recent history of pneumothorax (2nd episode) in a young heavy smoker patient with two episodes of right pneumothorax, one of which was recent, known with Diabetes mellitus and COPD, with imaging changes such as "reticulo-nodular lesions with cystic appearance and interstitial fibrosis on the left lung area" the diagnosis of COPD was questioned and the suspicion of pulmonary histiocytosis X was raised, for which reason, together with the radiologist and thoracic surgeon, the decision was made to surgically treat the pneumothorax under general anesthesia and oro-tracheal intubation and to perform a lung biopsy in order to establish a definite diagnosis. The surgical outcome was very good, with suppression of the drainage tube and discharge of the asymptomatic respiratory patient 10 days after admission.

Hematoxylin-eosin stained lung biopsy (image not available) identified a large number of typical Langerhans cells with intensely eosinophilic cytoplasm and irregular nuclei. Langerhans cells stained positive for CD1a. A centrilobular emphysema with intra-alveolar macrophage sloughing was also evident. Lung biopsy confirmed the suspicion of pulmonary histiocytosis X.



Since in histiocytosis X the damage is multi-organ, one month postoperatively the patient underwent a complex biological, functional and imaging evaluation to identify or exclude other affected organs. The usual biological assessment was within normal limits. In addition, alpha1 antitrypsin - 1.63 g/L (0.90 - 2.00 g/L) and serum angiotensin converting enzyme (ACE) - 32 U/L (12-68 U/L) were also determined and found to be within normal limits. Complex respiratory functional assessment at the age of 31 years, on which occasion the diagnosis of COPD was also established. Spirometry showed- FVC - 76.3%, FEV1 - 67.2% IT - 65.6%, MEF 50 - 31%, TLC - 94%, VR-138.5% - mild-moderate obstructive ventilatory dysfunction, with no response to bronchodilator. Lung diffusion capacity for carbon monoxide (DLco) in a single breath - Dlco - 51.8% - moderate decrease in alveolar-capillary diffusion.

Complex respiratory functional assessment was done in the sitting position using a bodyplethysmograph. From a functional point of view the following values were identified: spirometry - FVC - 73%, FEV1 - 68% IT - 77%, MEF 50 - 50%, - restrictive ventilatory dysfunction. No response to bronchodilator was noticed. Lung diffusion capacity for carbon monoxide (DLco) in a single breath and corrected for the patient's haemoglobin value. Dlco - 53.4% - moderate decrease in alveolar-capillary diffusion.

During the 6-Minute Walk Test (6MWT) test, the patient walked 87.27% of the predicted distance and desaturated 5 percentage points compared to the SpO2 (98%) measured at the start of the test. Dyspnea assessed using the Borg Scale identified initial dyspnea 1 and final dyspnea 3.

Nocturnal ventilatory polygraphy was performed at the patient's home using the Alice Night One polygraph. Summarized parameters of the nocturnal ventilatory polygraphy were as follows: TIB 469 minutes Ahi - 56/h, Di - 95/h, SpO2 minimum - 69%, SpO2 mean - 91%, SpO2<90% - 36%(TIB), SpO2<85% - 7%(TIB), SpO2<80% - 1%(TIB).

Published studies have shown that the most common lesions in histiocytosis have been identified in the skull and jaw bones, which is why imaging investigations have included bone scintigraphy and brain MRI. Bone lesions were not identified by scintigraphy and brain MRI showed no space-occupying lesions in the pituitary and hypothalamic glands. Pulmonary computed tomographic imaging evaluation revealed: interstitial pulmonary micronodules, predominantly in the upper and middle territories, thin-walled microcysts ranging in size from 3 to 12 mm, some with a tendency to confluence, fine fibrotic bands arranged subpleurally bilaterally, left kidney absent.

Given the evidence already published on the presence of pulmonary hypertension in

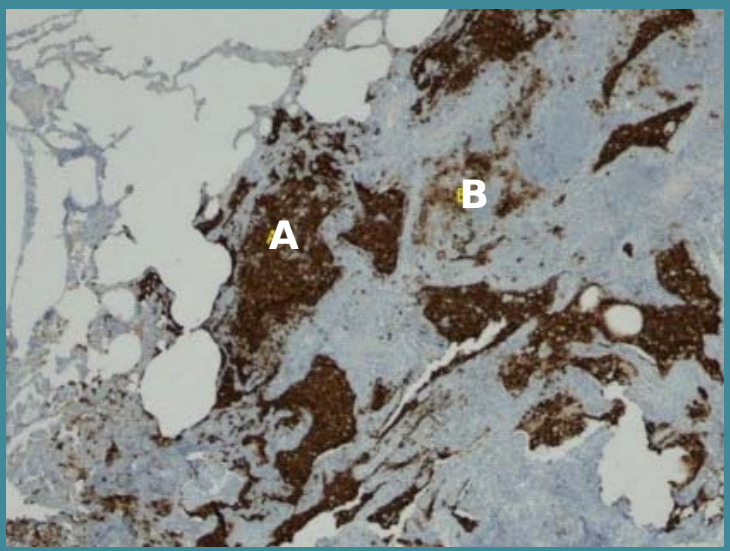


Figure 1. *Lung histologic pattern: Langerhans cells-(A) CD1a and (B) protein S100 positivity. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7403809 - Adult pulmonary Langerhans cell histiocytosis revealed by central diabetes insipidus: A case report and literature review. Jorge Lourenço, Cristina Ferreira, and Daniela Marado Mol Clin Oncol. 2020 Oct; 13(4): 30. Published online 2020 Jul 22. doi: 10.3892/mco.2020.2100. PMCID: PMC7403809. PMID: 32765877*

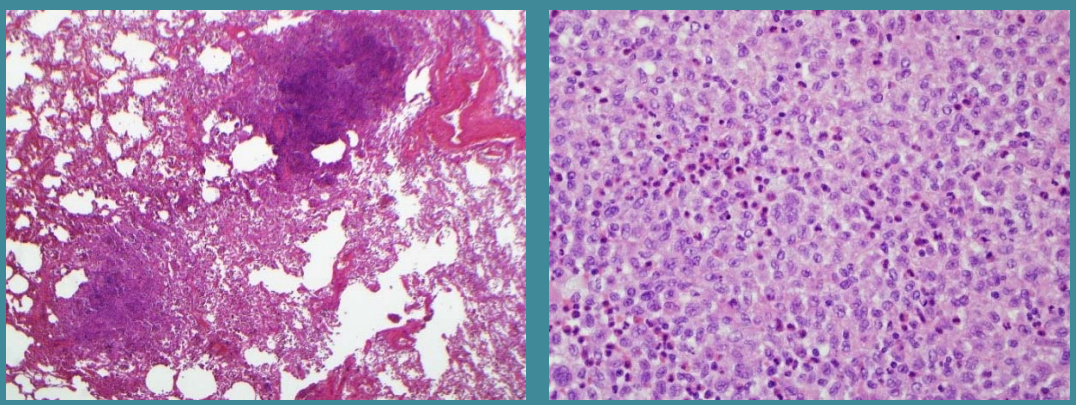


Figure 2. *Pulmonary Langerhans cell histiocytosis Harpreet S Suri1, Eunhee S Yi, Gregorz S Nowakowski and Robert Vassallo. https://ojrd.biomedcentral.com/articles/10.1186/1750-1172-7-16. Left image in haematoxylin-eosin stain - microscopic image capturing a nodular lesion centred on the airways. Right image in haematoxylin-eosin stain - diffuse infiltration of lung tissue with Langerhans cells and many eosinophils mixed among the Langerhans cells.*

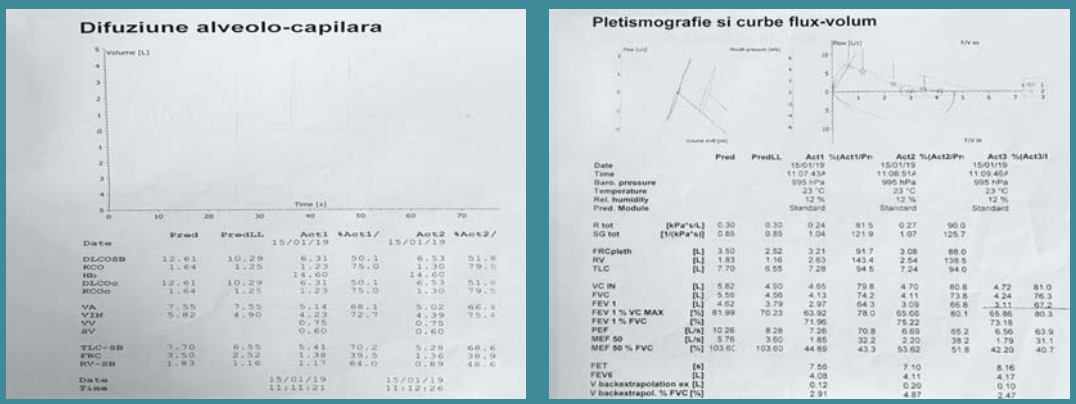


Figure 3. *Spirometry and DLCO – the patient's personal file*



patients with pulmonary histiocytosis X, we also subjected the patient to a resting and post-exertional cardiological examination (6-minute walk test), on which occasion transthoracic cardiac ultrasound was performed to measure the mean pulmonary artery pressure (mPAP). The results identified were: resting PAPm =28 mmHg and exercise PAPm =42 mmHg. Given the pulmonary artery pressure >25 mmHG at rest and >35 mmHG after exercise, the patient was recommended to undergo a cardiac catheterization at discharge (which he did not undergo).

Imaging and functional investigations performed, together with the patient's history, age and medical history, refuted the diagnosis of COPD. Thus, we formulated the following final diagnoses, accompanied by hygienic, non-pharmacological and pharmacological recommendations.

Final diagnoses: Pulmonary histiocytosis X. Severe obstructive sleep apnoea syndrome. Secondary pulmonary hypertension. Diabetes insipidus type II in treatment with ADO. Congenital single right kidney. Gout in treatment. Obesity grade II. In our patient, the diagnosis was based on a high degree of suspicion, in a young patient with a diagnosis of COPD and Diabetes mellitus, with repeated episodes of Pneumothorax, complemented by lung radiotomographic examination, histopathological examination of the lung and positive immunohistochemical tests for CD1A and S100 markers.

Treatment and recommendations

Therapeutically for pulmonary histiocytosis X it is recommended to stop smoking urgently. Since the patient was respiratory asymptomatic after surgical treatment of pneumothorax, the decision was made to stop treatment with Spiolto Respimat and monitor respiratory function at 6 months in the first year.

The patient continued to be respiratory asymptomatic at subsequent assessments, and respiratory function remained functionally stationary, which is why the patient remained on monitoring and without bronchodilator treatment. For obstructive sleep apnoea syndrome, he was recommended APAP 6-12 cmH2O positive pressure therapy with nasal mask administration. In addition to smoking cessation and weight reduction, the patient was recommended cardiological monitoring, given published evidence of increased risk of pulmonary hypertension in patients with pulmonary histiocytosis X. The evolution two years after the diagnosis of Pulmonary Histiocytosis X and smoking cessation was very good, with the patient maintaining respiratory asymptomaticity and functionally stable respiratory function. Obstructive sleep

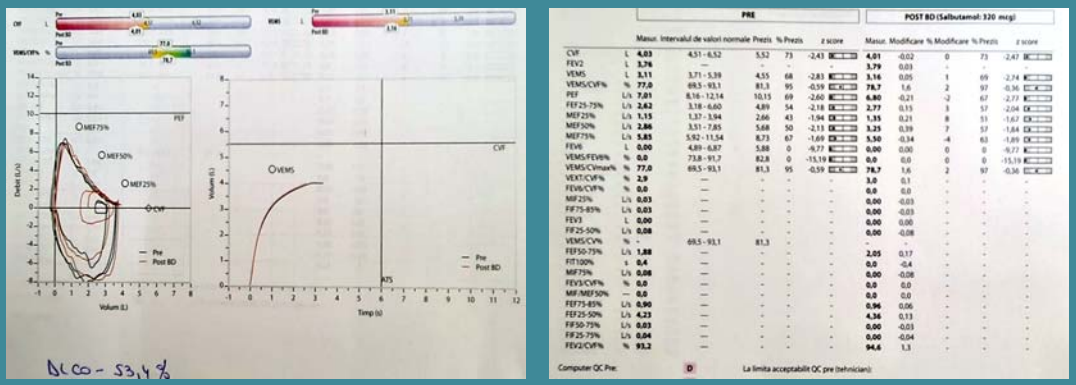


Figure 4. *Complex respiratory functional assessment of our patient*

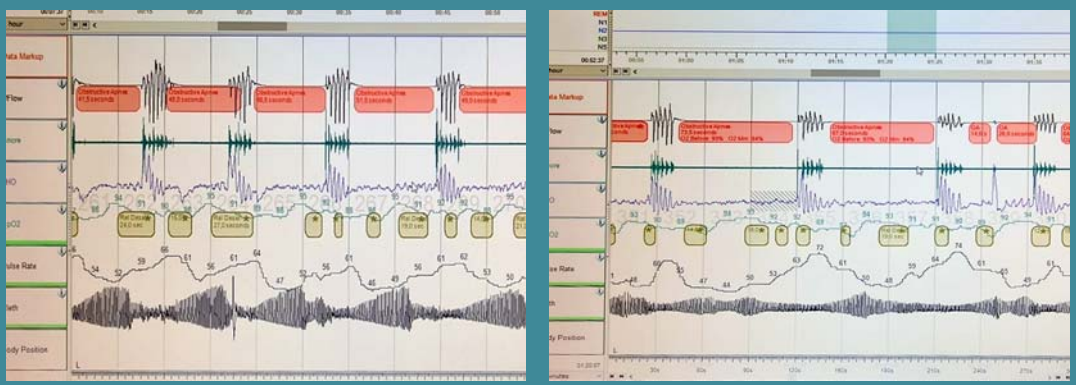


Figure 5. *Polygraphic evaluation of our patient*

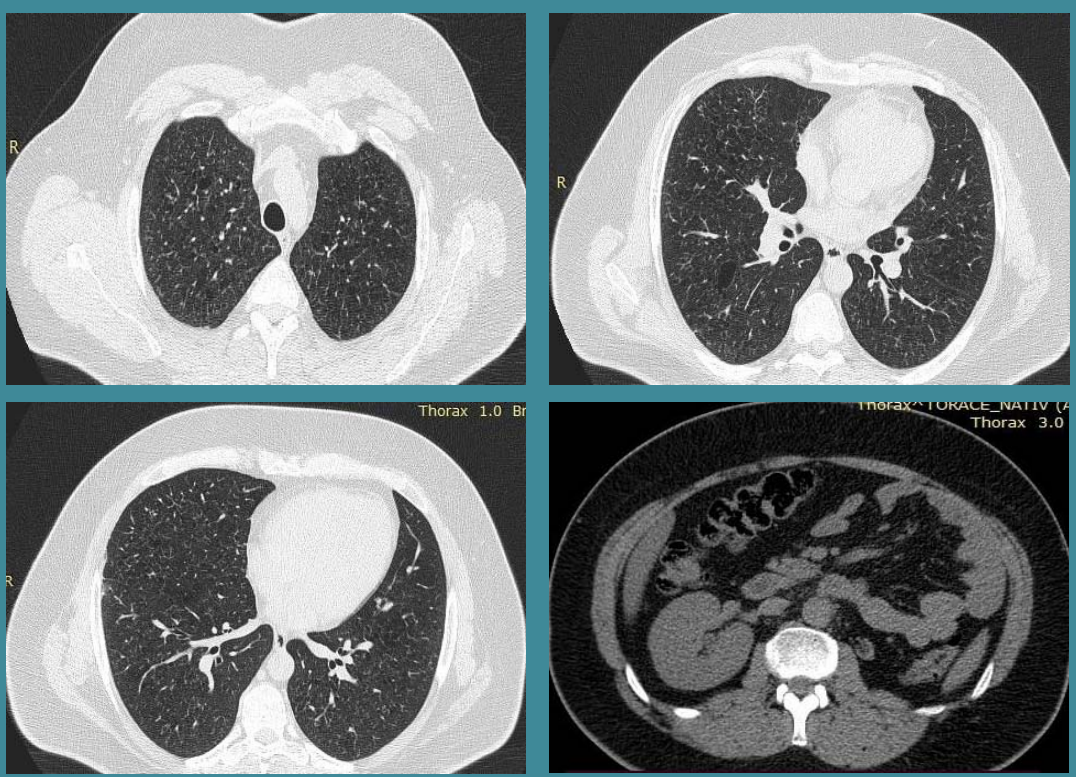


Figure 6. *Computed tomographic evaluation of our patient*



apnea syndrome being controlled under positive APAP pressure (Ahi - 0.7/h).

Particularity of the case

The particularity of this case was represented by the diagnosis of COPD at 31 years of age, based on smoking history and spirometry, without evaluation of alpha1-anthrypsin deficiency and without CT imaging evaluation in a patient with diabetes mellitus since the age of 19 years and history of right total pneumothorax at the age of 28 years.

A significant percentage of patients with pulmonary histiocytosis X are completely asymptomatic at diagnosis. The diagnosis is made by accident after an imaging or respiratory functional assessment, when evidence suggestive of lung disease is found, requiring further investigation. The most common symptoms reported by patients diagnosed with pulmonary histiocytosis X are: dry cough, exertional dyspnea, chest pain, physical asthenia, weight loss, decreased tolerance to physical exertion, fever, etc. Another category of patients diagnosed with this condition presents to the consultation or emergency room for sudden onset dyspnea secondary to a pneumothorax. Pneumothorax is a frequent complication, manifested by the rupture of a lung cyst in the pleural cavity and migration of air from the lung parenchyma to the pleural cavity. The form of presentation with pneumothorax at onset occurs in 15-20% of diagnosed cases. At other times, the diagnosis is made in a young, smoking patient who has been recently diagnosed with diabetes insipidus.

Clinically, it is almost impossible to raise suspicion of pulmonary histiocytosis X on the basis of features identified on clinical examination alone, especially in respiratory asymptomatic patients. In order to avoid misdiagnosis, a wide range of investigations is used. Imagistically, pulmonary histiocytosis X is characterised by bilateral, diffuse and predominantly lower 2/3 lung involvement. Nodular lesions of 2-12 mm can be identified on the chest X-ray, which may be cystic lesions, fibrotic lesions with a "honeycomb" appearance. Other times the chest X-ray shows a total or partial pneumothorax.

Chest tomography, being a far superior imaging investigation to chest X-ray, can characterize lesions and their extent much more realistically. The following are identified: thin-walled lung cysts, which are also the most common imaging presentation. Pulmonary nodules are the second most common presentation. Other forms of presentation may include: excavated nodules, thick-walled cysts, "frosted glass" appearance, "honeycomb" appearance. Periodic imaging evaluations in patients with pulmonary histiocytosis X demonstrated

transformation of nodular lesions to thick-walled and then thin-walled cysts. Complex respiratory functional assessment can most commonly reveal restrictive ventilatory dysfunction with identification of low lung volumes and low DLCO. However, there is also a percentage of about 20% of patients in whom obstructive ventilatory dysfunction and low DLCO are identified, a phenomenon blamed on smoking.

Diagnosis of the disease is rather difficult and sometimes requires a long time, but the patient's history, together with clinical examination, complex respiratory functional examination and lung CT images may raise the suspicion of pulmonary histiocytosis X, and then we have confirmation by bronchoalveolar lavage or histopathological and immunohistochemical examination. Bronchoalveolar lavage may identify Lagerhans cells with CD1a markers, containing intracytoplasmic X corpuscles visible by electron microscopy. On histopathological examination the basic lesion is nodular or lamellar clusters of H-X cells between which numerous eosinophils can easily be identified.

In pulmonary histiocytosis X, on histopathological examination, lesions are identified mainly vascular and perivascular, peribronchial, interstitial and in the subpleural septa. Rarely, the diagnosis can be made in the absence of an organic biopsy if a medulogram with CD1A antigen identification by immunohistochemical techniques or Birbeck granule detection by electron microscopy is performed. Antigenic markers reacting with CD1a glycoprotein, S100 cytoplasmic protein detected by immunoperoxidase staining and/or the presence of Birbeck granules on electron microscopic examination are required for a definitive diagnosis of pulmonary histiocytosis X.

Treatment depends on the severity and extension of the disease. Cessation of smoking and or prolonged exposure to cigarette smoke is the first effective therapeutic means of combating Pulmonary Histiocytosis X. Stopping smoking leads to halting the progression, sometimes even to regression of the lesions. Respiratory asymptomatic patients are only periodically monitored for imaging and function. In symptomatic or severely symptomatic patients with airway obstruction identified by complex respiratory function tests, bronchodilator therapy may be tried. In well-selected cases, treatment with corticosteroids and/or immunotherapy may also be tried. Oxygen therapy on the mask together with the rest of the drugs may be useful to relieve symptoms and improve quality of life. A limited category of patients may benefit from surgical treatment, which consists of resection of the affected area, and in severe forms of the disease affecting the whole lung, lung transplantation may be considered. The outcome of adult disease depends very much on the patient's smoking cessation behavior. There is much medical evidence that progression is halted or greatly diminished by smoking cessation, but there is also a small percentage of patients who develop severe obstructive pulmonary disease with the onset of respiratory failure even after smoking cessation. The onset of the disease in childhood with multiorgan damage is associated with a poor prognosis.

Discussion

Langerhans cell histiocytosis is a group of rare disorders characterized histopathologically by proliferation of Langerhans cells. It is a rare condition with an incidence of 1-2 cases per one million population among adults, but also



has an increased frequency among children. It is common in young people, with a peak incidence between the ages of 20 and 40. The etiopathogenesis of the disease remains unknown although several theories have been put forward, but many studies have demonstrated a strong association between smoking and the disease (Fartoukh et al., 2000)[1].

It has thus been concluded that smoking, if not a direct cause, is at least an important contributing factor. Simply quitting smoking can lead to remission in the absence of other treatment.

The disease is much more common in Caucasians and very rare in blacks. Any organ can be affected, but skin and bone are most commonly involved. The form with lung involvement is more common in males in strong association with smoking. The disease is manifested by proliferation and accumulation of Langerhans cells in the affected organs. In 1953 Lichtenstein proposed the name histiocytosis X to identify an all-embracing syndrome that included three distinct pathological entities: Hand-Schuller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma or pulmonary histiocytosis X. All are characterised by the accumulation of histiocytes. Association of multiple bone lesions with systemic, cutaneous, nervous system - pituitary gland, liver, ganglia, bone marrow locations are very common in Letterer-Siwe disease.

The association of multiple bone lesions, exophthalmos through retro-orbital granuloma and diabetes insipidus through hypothalamo-hypophyseal invasion are found under the name of Hand-Schuller-Christian disease. Proliferation of Langerhans cells predominantly in the lungs has been termed pulmonary histiocytosis X. The course of the disease is unpredictable, it may regress spontaneously or under treatment in association with smoking cessation, but in a minority of patients it may progress to pulmonary fibrosis and respiratory failure. Histopathological observations also suggested that pulmonary vascular involvement plays a central role in advanced pulmonary histiocytosis.

There is published evidence of the development of pulmonary hypertension in patients with advanced forms of pulmonary histiocytosis X (Fartoukh et al., 2000)[1]. Histopathological data strongly support this hypothesis. In all patients with pulmonary histiocytosis X, severe diffuse pulmonary vasculopathy involving both pulmonary arteries and veins was found. Such pulmonary vasculopathy probably also explains the severe reduction in DLCO and limitation of exercise capacity in patients with pulmonary histiocytosis X, which were disproportionate to the respiratory functional

changes (Crausman et al., 1996; Fartoukh et al., 2000)[1,2]. Histopathologically, pulmonary histiocytosis X is characterized by peribronchiolar infiltration with Langerhans cells, lymphocytes, plasma cells, neutrophils and eosinophils.

Frequently, Langerhans cells infiltrate the walls of medium and small pulmonary arteries (Crausman et al., 1996)[2]. Since the incidence and severity of pulmonary hypertension in advanced pulmonary histiocytosis X is much higher than in other chronic lung diseases, rigorous cardiological monitoring is also required.

No effective therapy has been developed for Pulmonary histiocytosis X except smoking cessation (Chang & Seale, 2006)[3]. Smoking cessation is likely to be the key treatment, leading to clinical improvement in about one third of subjects. Tobacco glycoprotein (TGP) is a potent immunostimulator that has been isolated from cigarette smoke. Youkeles et al. (Youkeles et al., 1995)[4] demonstrated that lymphocyte proliferation in response to TGP differs from the response of cigarette smokers without TGP and suggested that an altered immune response to TGP may be involved in the pathogenesis of the disease. However, the exact mechanisms by which tobacco may induce pulmonary histiocytosis X remain undetermined (Watanabe et al., 2001)[5].

Although there is no clear criterion for corticosteroid administration for this disease, steroid therapy may be indicated for patients with higher disease activity because pulmonary histiocytosis X is predominantly an interstitial lesion. The overall results of steroid treatment in patients with pulmonary histiocytosis X in Riko Watanabe's study (Watanabe et al., 2001)[5] are not encouraging. The category of tests important for the assessment of patients with respiratory and cardiac diseases also includes the six-minute walk test (6MWT) (Chang & Seale, 2006)[3]. It is a commonly used tool in cardiology and pulmonology services for the assessment of various interventions including pharmacological interventions, oxygen prescription, in rehabilitation programs, even in thoracic surgery services, because it is a tool that requires minimal patient training, is inexpensive and simple, well tolerated, can be performed without the need for high technology and targets exercise capacity in people with cardiac and or respiratory disease. It is a self-paced test that requires the patient to walk for six minutes, reflecting very accurately the daily activities that are performed by the patient at submaximal levels of exertion (Chang & Seale, 2006)[3]. A physician is not required to perform this test, but it is recommended that technicians performing the test be trained in cardiopulmonary resuscitation and that medications to treat angina, bronchospasm and severe respiratory distress be available for such situations (Enright, 2003)[6].

Conclusions

Pulmonary histiocytosis X is a rare disease that occurs in both adults and children. Although the pathogenesis of this entity has not yet been fully resolved, there is evidence supporting the idea of immune system dysregulation. In the case of pulmonary histiocytosis X we can draw an analogy with pulmonary sarcoidosis in that there is an active phase of variable duration followed by stabilization of lesions or even resolution in the majority of patients in the absence of treatment, and disease progression in a minority of patients (Colby & Lombard, 1983)[7]. As lung function can deteriorate in a



proportion of patients even after smoking cessation, respiratory functional assessment using parameters FEV1, FVC and DLCO at 6 months after diagnosis is recommended (Tazi et al., 2015)[8].

High-resolution chest computed tomography should be performed in all patients with interstitial changes evidenced by standard chest radiography, especially in smoking patients. In patients in whom chest CT identifies nodular and cystic lesions, investigations should be supplemented with bronchoscopy with bronchoalveolar lavage and/or lung biopsy for diagnostic certainty. More and more scientific evidence gives a central role to pulmonary vascular dysfunction in limiting exercise performance in patients with pulmonary histiocytosis X. Recent research suggests that vascular involvement may in fact be a central process underlying the pathophysiology observed in pulmonary histiocytosis X.

As concluded by Watanabe (Watanabe et al., 2001)[5], the therapeutic results obtained with steroids have been disappointing, even though steroids have been and still are considered to be a treatment of greatest benefit to this category of patients. Further studies are needed to shed light on prognosis and long-term survival. A critical component of the management of adults with pulmonary histiocytosis X is smoking cessation. This simple attitude can lead to disease regression or stabilization of symptoms although a limited category of patients will experience disease progression despite smoking cessation.

There are no biological markers that predict which patient will have a good progression and in which disease will continue to progress despite smoking cessation (Suri et al., 2012)[9].

Lung transplantation is a therapeutic option for a limited number of patients with progressive disease despite smoking cessation and failed attempts at immunosuppressive treatment. Lung transplantation should be considered in patients with severely ill, respiratory failure refractory to other forms of treatment, including patients with progressive pulmonary hypertension who do not respond to vasodilator therapy (Suri et al., 2012)[9]. The disease course is variable and unpredictable, ranging from asymptomatic to progressive debilitating disease with respiratory failure and death within a few years. Survival of patients with established pulmonary histiocytosis X is shorter than that of the general population.

Unresolved issues and future directions

Substantial progress has been made, but issues such as pathogenesis, clinical evaluation, and therapeutic management of patients with pulmonary histiocytosis X remain unclear and require further study. The

role of lymphocytes and eosinophils found in many nodular inflammatory lesions remains unclear and requires future attention. Future studies should clarify issues regarding more effective respiratory therapies in patients with disease progression, as well as effective vasodilator therapies in patients who also associate pulmonary hypertension. Unfortunately, the complexity of the disease and its rarity hinder research into more effective therapies and diagnostic mechanisms.

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