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Diagnosis of bronchiolitis obliterans organizing pneumonia after allogeneic bone marrow transplantation. Case report

Pathologically, organizing pneumonia is defined by the presence in the distal airways spaces of granulation tissue buds, fibrin exudates, and eventually collagen containing fibroblasts. Lesions occur predominantly within alveolar spaces but are often associated with buds of granulation tissue occupying bronchiolar lumen (bronchiolitis obliterans). Bronchiolitis obliterans with organising pneumonia (BOOP) was described by Epler et al. in 1985 as a clinicopathologic entity of unknown aetiology and rather good prognosis (7), and in 1983 Davison et al. had already reported eight cases with histological evidence of organizing pneumonia without microbiologic evidence of pathogen, i.e., cryptogenic organizing pneumonia (COP) (5).

Most cases of BOOP are idiopathic. They are also associated with connective tissue diseases, various immunodeficiency syndromes, graft-versus-host disease (GvHD), bone marrow transplantation (BMT), lung transplantation, viral infections, inhalation of toxic substances and treatment with a variety of drugs (6). The development of obstructive airway disease as a result of BOOP is an important problem after allogeneic BMT, but it has rarely been described after autologous transplantation. BOOP is present especially in patients with decreased post-transplantation immunoglobulin level, GvHD and cytomegalovirus (CMV) infection (11).

CASE REPORT

We report a 40-year-old female patient suffering from chronic myeloid leukaemia (CML), who in December 1999 underwent multidrug chemotherapy followed by allogeneic BMT with her HLA-matched sister as a bone marrow donor. One year after transplantation, recurrent bronchial and lung infection symptoms appeared and were inefficiently treated with antibiotics. The main symptoms were dry cough with shortness of breath and fever.

In February 2001, the patient suffered from hepatitis leading to hepatic insufficiency, which resulted from mixed infection with HBV, HCV, Epstein-Barr virus and *Varicella zoster* virus. IgM antibodies against cytomegalovirus (CMV) were also ascertained. At the same time, GvHD symptoms such as keratoconjunctivitis, candidiasis of oesophagus and bronchus bacteraemia, caused by *Staphylococcus aureus*, as well as deterioration of liver function with increased level of GGTP (894 U/l) appeared. Because of respiratory failure, it was necessary to apply assisted breathing. Chest computed topography (CT) revealed multiple pulmonary nodules and airy reduction suggesting intraalveolar and intrabronchioli infiltration. The patient was treated with antibiotics, anti-viral and anti-mycotic medications and chronically with Encorton in a dose of 20 mg/24 hours. However, symptoms of CML were not identified.

Since that time, health improvement was observed, but from June 2001 to January 2002 the patient was hospitalised seven times because of recurrent pneumonia. *Streptococcus* sp., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenze* and *Candida albicans* were detected in bacteriological culture of sputum and bronchoaspirat. Despite three-time-conducted bronchoscopy, histopathological analyses were not performed. At that time the patient was treated with a combination of different antibiotics and inhalant steroids.

In February 2002, the patient was hospitalized in the Pulmonary Department of the Medical University of Lublin due to progressive dyspnoea (oxygen saturation of 87.3%), cough with purulent expectoration and fever. Physical examination revealed inspiratory crackles and wheezing. The symptoms of GvHD such as cachexy, xerodermia, hair loss and kerato-conjunctivitis remained.

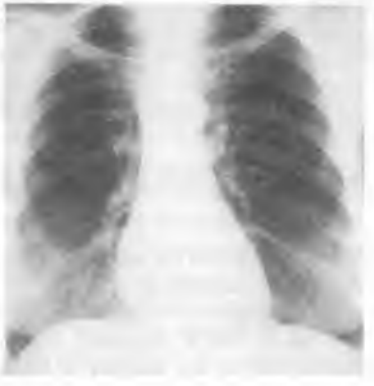

Fig. 1. Typical imaging pattern of BOOP linear opacities in the lower lung areas

Pulmonary function tests (PFT) revealed their gradual deterioration characterized by irreversible airflow obstruction and reduction of the vital capacity (FEV1 of 14.8% of the predicted normal values (PV), VC of 24.0% of PV and FEV1/VC – 52.2% of PV) and of blood gas parameters (PaO_2 of 53.1 mmHg and $PaCO_2$ of 42.2 mmHg), all of which confirmed hypoxemia and respiratory failure. Area of increased lung translucency and of irregular linear opacities in the lower lung areas were detected in chest-X-ray examination (Fig. 1). Blood cell count revealed an increased number of leukocytes (29.200 cells/mm^3) with predominance of polymorphonuclear granulocytes (93.4%). In a bacteriological culture of sputum, *Burkholderia cepacia*, *Psuedomonas aeruginosa*, *Staphylococcus* sp., *Streptococcus* sp. and *Candiada* sp. were detected. Serological analysis, performed in order to determine the presence of systemic mycosis, gave a negative result. Markers of liver function remained at the normal level. Intensive antibioticotherapy was applied, regarding antibiotic sensitivity of bacteria: Biocefal, Amikin against *Burkholderia cepacia*, Doxocyclin, Tazocin, Abactal against *Pseudmonas aerruginosa* and Orungal against *Candiada* sp. Regression of acute inflammatory symptoms, which manifested as absence of fever and purulent expectoration as well as normalization of clinical results were obtained. However, dry cough and auscultatory phenomena did not disappear and the patient's respiratory failure persisted (PaO_2 of 65.1 mmHg and $PaCO_2$ of 36.8 mmHg).

Chest CT showed the presence of diffused areas characterized by decreased density and hypoperfusion (Fig. 2). The examination revealed aggregations of irregular nodules of lung tissue: four of the diameter of 3.5 cm in the left lung and two smaller in the lower area of the right pulmonary lobe. Infiltration of lung parenchyma in pulmonary hilus was also present.

Immunological flow cytometry analysis of lymphocyte subtypes, performed after normalization of morphological results, indicated a high percentage of cytotoxic T cells (15.9%) representing 64.9%

Fig. 2. Diffuse airspace consolidation on computed tomographic scan

of CD8+ T lymphocytes. The patient's condition did not make it possible to conduct bronchoscopy and obtain material for histopathological examination.

Persistence of symptoms after elimination of infectious pneumonia, insufficiency of antibiotic therapy and typical image of CT led to BOOP diagnosis. Typical symptoms, identification of opportunistic infection and abnormalities in the analysis of immunological response indicated GvHD. Therefore, the patient was treated with steroids: initially with intravenously administered methylprednisolone in a dose of 120 mg/day for the first two days and than 40 mg/day for five days before changing to oral steroids (Metypred) in a dose of 12 mg/day. The clinical condition improved and respiratory failure regressed (PaO_2 of 78.3 mmHg, $PaCO_2$ of 38.0 mmHg and oxygen saturation of 96.3%).

DISCUSSION

Soubani et al. reported that pulmonary complications appeared in 40–60% of patients who received BMT, where BOOP was diagnosed in 2–13% of these. That review classified BOOP as a late alteration, which may occur any time after 100 days after transplantation. At the same time, they observed characteristic symptoms leading to fatal respiratory failure with an overall mortality up to 65% three years after transplantation (12).

In the described patient, symptoms of BOOP appeared one year after BMT. Initially, they resembled those of upper respiratory tract infection. There were no data regarding the results of the pulmonary function tests and CT examination. It excluded the possibility of certain diagnosis of BOOP. Fifteen months after BMT, the patient's condition deteriorated due to viral and mycotic infections and chronic GvHD symptoms. The presence of antibodies against CMV and appearance of opportunistic pathogens as *Candida* sp. and *Burkholderia cepacia* were worth noticing. Cytomegalovirus pneumonia usually appears six to 12 weeks after transplantation and involves 10 to 40% of bone marrow recipients. The fatality rate because of CMV pneumonia is 85%, but the combination of ganciclovir and high doses of immunoglobulins may contribute to survival improvement. The lack of dramatic course of the disease in our patient excluded the pneumonia of a CMV aetiology (12). Leblond V. et al. described late CD8+ lymphocytic alveolitis after allogeneic BMT and chronic GvHD (9). On the other hand, it is know that viral infection caused by CMV, autoimmune process directed against the bronchial tree and damage of small airways

secondary to GvHD may induce BOOP. Therefore, viral infection may have resulted from the activation of the host's cell-mediated response (2). These data suggest that BOOP reflect the response to an initial unclear injury causing pulmonary inflammation, which is further self-perpetuated to produce the characteristic intra-alveolar granulation tissue (10,11).

At this time, chest CT indicated abnormalities such as airspace consolidation and irregular nodules in both lungs. Airy reduction in CT scans may suggest BOOP diagnosis but multiple pulmonary nodules may indicate an infection of a probable mycotic aetiology as well. We obtained similar CT image one year later. Alasaly et al. classified the patterns of CT abnormalities in BOOP as airspace consolidation, ground-glass attenuation, nodules and irregular linear opacities. Nodules were defined as being less than 5 mm, 5–10 mm or 10–20 mm in diameter. Consolidation was the main finding in 68% and nodules in 20% of patients. The alterations were observed in all lung areas, but irregular linear opacities in chest-X-ray were only seen in the lower lung area in 16% of patients (1). Epler described the patients with idiopathic BOOP, who had multiple large nodules or masses in chest CT. The number of masses varied from two to eight. The authors concluded that BOOP should be considered when multiple large nodular lesions have been found in chest CT showing air bronchograms, irregular margins, broad pleural tags, parenchymal bands or subpleural lines. Multiple nodular BOOP has become a clinically important process, especially because it might be indistinguishable from carcinoma metastases or infections (6).

The results of pulmonary function tests in our patient were in accordance with literature data concerning BOOP. Those studies revealed the presence of a combined obstructive and restrictive pattern in most patients. The predominant PFT pattern was characterized by obstructive (reduced FEV1) with a variable restrictive component (reduced VC). Analysis of blood gases indicated mild or major hypoxemia with a normal $PaCO_2$ value in most patients (3, 4). However, in chronic GvHD bronchiolitis obliterans, which is not the same as BOOP, may produce severe obstructive airway disease with a normal chest radiographs. The patients suffering from this illness poorly respond to treatment and the disease can lead to progressive hypercapnia and death (8).

Unfortunately, three times performed bronchoscopy did not make it possible to obtain histopathological results. When in our Clinic, the patient's condition was too serious to perform the lung biopsy. Most of the authors considered that BOOP diagnosis should be mainly based on pathologic findings on lung biopsy. The video-assisted thoracoscopy is a preferred technique for diagnosing BOOP, since it provides quite large lung specimens. Transbronchial lung biopsy specimens may help to identify BOOP in many cases, but they do not enable an adequate exclusion of associated lesions or disclose clues to a cause of the process. However, Cordier ascertained that the diagnosis of BOOP without a biopsy is seldom justified. It may be considered in patients who are critically ill or if the clinical diagnosis is considered as highly probable by the physicians and if the improvement with high doses of corticosteroids has appeared (3).

Appropriate immunosupressive therapy may have an impact on the evolution of this disease. Some authors suggested that high doses of methylprednisolone sodium succinate (Solu-Medrol) and cyclosporine are efficient in restraining the disease. The literature data led us to BOOP diagnosis in our patients and to suitable treatment. They seem to confirm the importance of early diagnosis of BOOP and effectiveness of steroidotherapy after eliminating accompanying infections.

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SUMMARY

We report the case of a 40-year-old female patient after allogeneic bone marrow transplantation due to chronic myeloid leukaemia. One year after transplantation, the symptoms of recurrent bronchial and lung infections, inefficiently treated with antibiotics, appeared. The disease was further complicated due to hepatic insufficiency resulting from mixed infection with HBV and HCV as well as because of chronic graft-versus-host disease (GvHD). Chest computed tomography and pulmonary function tests seemed to confirm BOOP diagnosis, but despite three-time-conducted bronchoscopy, histopathological diagnosis was not obtained. When admitted to the Pulmonary Department, the patient was in serious condition caused by intensifying respiratory failure. After multidrug therapy enabling to control opportunistic infections, high doses of corticosteroids were administered intravenously resulting in partial health improvement. The patient seems to be afflicted with BOOP of mixed aetiology. Treatment efficiency may confirm the necessity of rapid BOOP diagnosis even if histopathological diagnosis is not obtainable.

Rozpoznanie zarostowego zapalenia oskrzelików z organizującym się zapaleniem płuc po alogenicznym przeszczepie szpiku. Opis przypadku

Opisujemy tutaj przypadek 40-letniej pacjentki, u której objawy zapalenia płuc, nie ustępujące po intensywnej antybiotykoterapii, pojawiły się w rok po alogenicznym przeszczepie szpiku, wykonanym z powodu przewlekłej białaczki szpikowej. Obraz chorobowy został dodatkowo skomplikowany w wyniku pojawienia się ostrego zapalenia wątroby, spowodowanego wirusami typu B i C, zakażenia cytomegalowirusem oraz wystąpienia objawów przewlekłej choroby przeszczep przeciw gospodarzowi. Tomografia komputerowa i badania czynnościowe płuc wydawały się potwierdzać diagnozę BOOP, ale pomimo trzykrotnej bronchoskopii nie otrzymano rozpoznania histopatologicznego. W momencie przyjęcia do Kliniki Chorób Płuc i Gruźlicy AM w Lublinie, w dwa i pół roku po przeszczepie, pacjentka była w stanie ciężkim z powodu narastającej niewydolności oddechowej. Po zastosowaniu wielolekowej terapii, umożliwiającej opanowanie infekcji oportunistycznych, podano dożylnie wysokie dawki kortykosterydów, uzyskując częściową poprawę zdrowia. U opisywanej pacjentki BOOP miał prawdopodobnie mieszaną etiologię. Skuteczność postępowania terapeutycznego może potwierdzać konieczność szybkiego rozpoznania BOOP, nawet przy braku potwierdzenia diagnozy w analizie histopatologicznej.