Non-infectious pulmonary complications in patients after the hematopoietic stem cell transplantation (HSCT)

Poster No.: C-0258
Congress: ECR 2015
Type: Educational Exhibit
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Keywords: Transplantation, Complications, CT-High Resolution, Lung
DOI: 10.1594/ecr2015/C-0258

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Learning objectives

To present the summary of current knowledge of non-infectious pulmonary complications (NIPC) after the hematopoietic stem cell transplantation (HSCT), the results of imaging methods and differential diagnosis of pulmonary abnormalities in immunocompromised patients.
Background

Pulmonary complications after HSCT are the most common and the most significant complications in terms of long term prognosis. A timely diagnosis and follow-up therapy are crucial for the further welfare of the patients. There are many factors which have an influence on the incidence of pulmonary complications. The type and the duration of the immunological deficit linked with the primary disease are the most important factors; other factors are the type of pre-transplantation preparations and the grade of immunosuppression, prophylaxis and therapy of infectious complications and also the possible development and therapy of the Graft versus host disease (GVHD). Complications occur more often after allogeneic than autologous transplantations. Peripheral blood stem cell transplantation is associated with significantly higher incidence of NIPC than bone marrow transplantation and cord blood transplantation [1].

Pulmonary complications can be classified according to the causing factors into infectious and non-infectious complications. In the past, there was an equal ratio of infectious and non-infectious pulmonary affections; but in recent years there has been a higher rate of non-infectious complications, which has been caused by efficient anti-infectious drugs - so these must be included in the differential diagnosis of pulmonary lesions.

We review NIPC following HSCT giving brief characteristics, imaging features and differential diagnosis in immunocompromised patients. The authors demonstrate some pulmonary pathology in high-resolution computed tomography (HRCT) that they encountered in their patients.
Findings and procedure details

HRCT is an excellent method for imaging the pulmonary affection; the problem is in its lower specificity [2,3]. Pulmonary complications often reflect the immunological status of the patient and they occur with the maximum incidence in a specific time period after the transplantation, and as such it is very useful for diagnostics to divide the complications into early ones (neutropenic phase 0-30 days and then phase 30-100 days) and late ones (> 100 days after HSCT) [4]. Immune functions improve gradually; a complete improvement usually comes in 6 - 12 months.

In the neutropenic phase (0- 30 days after HSCT), the frequency of non-infectious causes of pulmonary complications is 50-80%. The most common complication is pulmonary edema, diffuse alveolar hemorrhage (DAH) and pulmonary toxicity syndrome (PTS). In the early phase after the engraftment (30-100 days) the most significant NIPC is idiopathic pneumonitis syndrome (IPS) and periengraftment syndrome (PES). Of infectious complications during the neutropenic phase bacterial infections are the greatest threat. After engraftment of the granulocytes there are viruses and fungal infections. In the late phase after HSCT the frequency of NIPC is also greater than infectious complications. In particular, bronchiolitis obliterans (BO), cryptogenic organizing pneumonia (COP) and delayed pulmonary toxicity syndrome (DPTS) occur. (Tab.1) To determine a non-infectious complication, infection must always be excluded (by blood culture, sputum culture, fibrobronchoscopy with bronchoalveolar lavage - BAL).

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Tab.1. Approximate timeframe of non - infectious complications after HSCT
Pulmonary edema

Pulmonary edema is a common complication, especially in the first two weeks after transplantation. It can be cardiogenic or non-cardiogenic, or it can also be combination of both of these. The cause of the pulmonary edema can be fluid overload or cardiotoxicity or nefrotoxicity of the chemotherapy (CHT) [5]. Pulmonary edema is in most cases already diagnosed by a chest X-ray; it usually disappears very quickly after the therapy (by controlling the income and outcome of the fluids, by the usual therapy in cardiac patients). (Fig.1). Differential diagnostics: We must exclude other causes of the alveolar radiographic abnormalities: pneumonia, DAH, hypersensitive pneumonitis (which can be a manifestation of pulmonary toxicity), idiopathic pneumonitis syndrome, aspiration pneumonitis (unilateral affection with predilection for the right side); and also bronchoalveolar carcinoma as a tumorous lesion.

Diffuse alveolar hemorrhage (DAH)

DAH is a life-threatening complication. It usually occurs in the second or third week after HSCT. The characteristic clinical symptoms are sudden progressive dyspnea, unproductive cough, fever, hypoxia requiring oxygen therapy.

Chest X-ray and HRCT: the initial radiographic pattern can be interstitial or alveolar involving the central portion of the lung, primarily the middle and lower lung zones. Radiographic abnormalities rapidly progress into severe diffuse bilateral alveolar process [6] (Fig.2). In differential diagnostics, we must exclude other alveolar abnormalities, especially pulmonary edema, pneumonia, IPS, PTS. Blood sample findings by BAL is typical.

DAH also appears as part of other diseases: Granulomatosis with polyangiitis (formerly known as Wegener’s Granulomatosis), Goodpasture syndrome, systemic lupus erythematosus, vasculitides, IgA neuropathies and other rare causes.

Idiopathic pneumonitis syndrome (IPS)

Idiopathic pneumonitis syndrome is a diffuse pulmonary affection. In practice it is observed that in most cases the pneumonitis, which occurs in the first 28 days after HSCT, is usually IPS [7]. Etiology of the IPS is multifactorial: the toxicity of the preparation before HSCT-chemotherapy (CHT), total body irradiation (TBI), immunological mechanisms. Clinical symptoms include dyspnea, unproductive cough, hypoxemia, but may also be negative or on the other hand may develop into acute respiratory distress syndrome.
HRCT: the image is unspecific, it includes bilateral extensive ground glass opacities (GGO) in diffuse or spotted distribution or migrating opacities, bilateral transient pulmonary infiltrates (multilobar finding in most cases), interstitial edema in association with interlobular septal thickening, pleural effusions (Fig.3). IPS is mostly diagnosed indirectly by excluding an infectious or other non-infectious etiology (edema of another etiology, DAH, PTS) [8].

**Pulmonary toxicity syndrome (PTS)**

Treatment induced pulmonary affections in patients who underwent high-dose cytostatic CHT and total body irradiation (TBI). Clinical findings are minor, mild shortness of breath, cough, fever; often an unexpected finding from radiological examination. It usually manifests 2 - 3 months after actinotherapy as radiation-induced pneumonitis.

HRCT: The most common sign is hypersensitive pneumonitis with bilateral poorly bounded confluent GGO, there can also be pulmonary consolidation presented (Fig.4). A less frequent sign is non-cardial pulmonary edema, affection of nodular character or bronchiolitis obliterans - like the image [9]. Changes have a predilection for localization in upper segments of lower lobes; they can gradually subside or progress into pulmonary fibrosis. Differential diagnostics include other alveolar abnormalities again: pulmonary edema of another etiology, ARDS, pneumonia, DAH, IPS.

**Periengraftment syndrome (PES) and Periengraftment respiratory distress syndrome (PERDS)**

PES is also termed a syndrome of autoagression. It usually appears in 3-5 days after the engraftment of the granulocyte line. Differentiation from acute GVHD is very difficult or even impossible [10]. HRCT shows thickening of interlobular septa, bilateral extensive GGO and confluent ill-defined pulmonary infiltrates, especially localized around pulmonary hili and also showing peribronchial distribution (Fig.5). The assessment condition for the diagnosis of PES is the presence of three major criteria or two major and at least one of the minor criteria. Major criteria are: diffuse alveolar abnormalities on the chest X-ray, HRCT or hypoxemia, skin affection of more than 25% of the body surface, temperature higher than 38°C, when infection is excluded. Minor criteria are: weight gain, hepatal dysfunction, renal dysfunction, transient encephalopathy [7,11].

**Pulmonary cytolytic thrombi (PCT)**

This is a rare condition characterized histologically by occlusive vascular lesions and hemorrhagic infarcts and clinically by a favorable outcome. It is possible that this unit represents the manifestation of acute GVHD in the lungs [12]. Typical clinical symptoms
are a fever and cough. The occurrence of PCT is usually in 6-11 weeks after HSCT. There are peripheral pulmonary nodules (usually several millimeters in size, rarely centimeters) on the HRCT.

In the differential diagnosis of pulmonary nodules, infectious causes must be excluded, especially Aspergillosis and other rarer mycosis; septic emboli or typical vascular thrombemboli. The differential diagnosis also includes primary tumors and metastases, while multiple pulmonary affection is more likely to suggest a metastatic process. Nodular lesions can also manifest in post-transplantation lymphoproliferative disease, which is very often associated with adenopathy and multiorgan affection.

**Bronchiolitis obliterans (BO)**

Bronchiolitis obliterans is a late complication, usually appearing 6-12 months after HSCT. It is a serious NIPS contributing to treatment-related morbidity, 40% mortality is reported. BO especially occurs in patients after allo-transplantation, sometimes in relation with chronic GVHD. BO is defined as an obstructive pulmonary defect clinically manifested by dyspnea on exertion, cough, or wheezing. Pulmonary function tests demonstrate an obstructive disorder of ventilation [13]. The chest X-ray can be normal or it can show minimal changes, there can be signs of hyperinflation, recurrent pneumothoraces or transient focal or diffuse opacities.

HRCT: Evidence of air trapping, small airway thickening, bronchiectasis, reduced pulmonary vascular branching or centrilobular opacities (Fig.6). Absence of respiratory tract infection [14].

**Cryptogenic organizing pneumonia (COP)**

COP, previously known as bronchiolitis obliterans organizing pneumonia (BOOP), is a significant late NIPC, but the pathogenesis has not yet been explained. Clinical symptoms include an unproductive cough, subfebrile temperature and dyspnea. Diagnosis of COP/BOOP is based on clinical restrictive dysfunction, radiological assessment and histological examination. A link with acute and chronic GVHD and COP has been revealed (15). On the chest X-ray there are spotty consolidations in more lobes presented.

HRCT: In most cases GGO, spotty nonsegmental consolidations and linear opacities with upper lung predominance are presented [16] (Fig.7). Another finding is thickening of pleura and pleural effusion. Less common findings have also been described, such as migrating opacities (similar to those which are presented in hypersensitive pneumonitis), multiple small nodules, focal solitary lesions, which can imitate bronchial carcinoma and nodules with cavities.
In differential diagnosis, we must exclude classic BO, in case of COP pulmonary function tests demonstrate a restrictive disorder of ventilation there is no obstructive disorder. In case of expansive consolidation, it can be difficult to distinguish bronchial carcinoma. On the other hand, multiple spotty opacities can be associated with bronchioalveolar carcinoma, lymphoma, vasculitis or pulmonary hemorrhage. In case of COP, the multiple small nodules must be distinguished from sarcoidosis or acute infectious bronchiolitis.

Delayed pulmonary toxicity syndrome (DPTS)

This includes drug-induced and radiation-induced changes, which progress into pulmonary fibrosis of various extent. Incidence depends especially on dosage and type of drugs (applied in preparation period before HSCT). [17].

HRCT shows changes from fine fibrous linearities, peribronchial thickening with traction bronchiectasis to pulmonary destruction with forming of cysts surrounded by thickened fibrous walls (honeycomb lung). Honeycomb lung is best seen on the periphery of the affected region of the lung (Fig.8). Pulmonary fibrosis is also a terminal stage of other pulmonary processes.

It is necessary to distinguish from the above described NIPC after HSCT the infectious complications and other conditions that may have similar appearance:

- Tumorous lesions included metastases (solid tumors, hematological malignities)
- Post-transplantation lymphoproliferative disease
- Pulmonary alveolar proteinosis
- Embolism: typical: consequence of hypercoagulation status
Images for this section:

**Fig. 1:** Pulmonary edema. HRCT demonstrates alveolar increased attenuation in perihillosal zones, patchy areas of ground glass opacities and fluidothorax bilaterally.

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**Fig. 2:** Diffuse alveolar hemorrhage (DAH). HRCT showes diffuse alveolar increase attenuation and consolidation, fluidothorax bilaterally.

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**Fig. 3:** Idiopathic pneumonitis syndrome (IPS). HRCT demonstrates interstitial edema associated with interlobular septal thickening, and patchy areas of ground glass opacities and ce-trilobular opacities bilaterally.

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**Fig. 4:** Pulmonary toxicity syndrome (PTS). HRCT showes bilateral extensive confluent ground glass opacities.

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**Fig. 5:** Periengraftment syndrome (PES). HRCT shows interstitial edema associated with interlobular septal thickening and alveolar edema in basal zones. Fluidothorax bilaterally.

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**Fig. 6:** Bronchiolitis obliterans (BO). HRCT demonstrates bronchiectasis, small airway thickening, pleural effusion. Pneumothorax on the right side.

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**Fig. 7:** Cryptogenic organizing pneumonia (COP). HRCT shows patchy areas of increased attenuation with upper lobe predominance bilaterally.

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**Fig. 8:** Delayed pulmonary toxicity syndrome (DPTS). HRCT demonstrates peribronchial thickening with traction bronchiectasis and pulmonary destruction - honeycomb lung.

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Conclusion

Imaging methods such as chest X-ray and foremost HRCT significantly contribute to the discovery of pulmonary pathology, the sole problem is the low specificity of pathological findings. Since the pulmonary complications often correspond to the type of immunodeficiency, the diagnostic image has to be considered in the relation to the time period elapsed after the transplantation and together with the clinical and laboratory findings.

The multidisciplinary approach to the pulmonary complications is crucial and consists of cooperation among haematologists, radiologists, pneumologists and pathologists.
Personal information

The work has been supported by the grants RVO-VFN64165 and PRVOUK-P27/LF1/1.

2. Wijersa SC, Boelensb JJ, Raphaelb MF, Beeka FJ, de Jonga PA. Does high-resolution CT have diagnostic value in patients presenting with respiratory symptoms after hematopoietic stem cell transplantation? Eur J Radiol 2011; 80:e535-e543

3. Versluys AB, Bierings MB, Beek FJ, Boelens JJ, van der Ent CK, de Jong PK. High-Resolution CT can differentiate between alloimmune and nonalloimmune lung disease early after Hematopoietic Cell Transplantation. AJR 2014;203:656-661


