Lung Delayed Hypersensitivity
A case with particular features

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Delayed hypersensitivity reactions are inflammatory reactions initiated by mononuclear leukocytes. These reactions are mediated by T cells and monocytes/macrophages rather than by antibodies. We describe a case of 50 years old man with lung type IV hypersensitivity. The case of lung delayed hypersensitivity presented has some particular histopathological and immunohistochemical features. The diagnosis of lung delayed type hypersensitivity requires analysis of correlation between clinic, radiographic, physiologic and pathologic criteria

Keywords: hypersensitivity reactions, mononuclear leukocytes, histopathological features

The original debate about the role of cell mediated and humoral immunity began in the 19th century between the French cellularists, led by Elie Metchnikof and the German humoralists. The humoralists believed that immunity was due to serum factors (antibodies and complement) which directly destroyed bacteria [1]. The cellularists believed that phagocytes were the basis for immunity. The 1940's experiments confirmed that both theories were essentially correct. Immune function is chemical (antibodies, complement) and also cellular (T cells, B cells and macrophages). Robert Koch was the first who demonstrated a delayed type hypersensitivity reaction in 1882 [2]. Coombs and Gell classified delayed type hypersensitivity as type IV [3]. Delayed hypersensitivity reactions are inflammatory reactions initiated by mononuclear leukocytes. These reactions are mediated by T cells and monocytes/macrophages rather than by antibodies. Both the CD4+ and CD8+ fractions of T cells have been shown to modulate a response. Were demonstrated four types of delayed hypersensitivity reactions based on the T-cell subpopulation involved: IVa- type 1 helper T cells, IVb- type 2 helper Tcells, IVc- cytotoxic T cells, IVd- IL8 secreting T cells. Th 1 cells mediate delayed-type hypersensitivity (DTH) trough secretion of ITF Yand IL-2. Disorders involving type IV reactions include contact dermatitis (eg, poison ivy), hypersensitivity pneumonitis, allograft rejection, tuberculosis, and many forms of drug hypersensitivity [4].

Contemporary debate regarding the reaction is focused on the role of the Th1 and Th2 cells originally discovered by Mosmann [5].

In delayed-type hypersensitivity reactions sensitized T cells mediate a cascade of cellular interactions. Initiation of these responses depends of vasoactive mediators from mast cells that are activated by antigen-specific T-cell-derived factors. Askenase and Loveren [6] discussed how this event initiates a sequence of steps that lead to T-cell recruitment of effector cells; and how this event differs from activation of mast cells by IgE antibody. They suggested that the conventional time-based separation of immediate and delayed hypersensitivity should be replaced by a classification based on the type of antigen-specific lymphocyte - B or T-responsible for the effects of hypersensitivity.

Refer to delayed hypersensitivity expression in the lung it was described hypersensitivity pneumonitis (extrinsic allergic alveolitis), an allergic lung syndrome considered to be a mix of type III and type IV hypersensitivity responses. It is caused by inhalation exposure to a wide variety of organic dusts. These dusts contain antigenic substances, including fungal/bacterial components, serum proteins and some chemicals.

Experimental part

Case presentation

A 50-year-old white male with cough, fever, signs of mild respiratory failure. Computed tomography (CT) scan of the chest demonstrated the mediastinal lymph nodes with the following dimensions: 2cm in the right paratracheal area, 0.6 cm in the lung hila and 1.7 cm infracarinal. Disabling, fibrous lesion, antero- basal, left lower lobe. Subpleural, bilateral, pulmonary ground glass opacities were noticed. Trachea and main bronchus were permeable. Hearth presented normal aspect. Pulmonary artery, thoracic aorta have normal caliber. Adrenal glands with normal aspect were found.

An open lung biopsy of the lingula and basal pyramid (paracardiac segment) was performed. Haematoxylin eosin staining indicated a biopsy from peripheral parenchyma with multiple lymphoid follicles separated one from each other. Focally we noticed severe bronchioalveolar destruction. We found alveoli irregular distension, massive accumulation of macrophages in the alveolar lumen, focally associated with edema, a high number of intravascular and extravascular eosinophils without a significant fibrosis. Occasionally, the blue corpuscles were present. The dusty macrophages were rare, crowded in small groups, perivascular, predominantly. The silver staining revealed a normal reticulin network in perivascular area and lung septa but disorganized in massive inflammation areas. The reticulin network was presented around lymphoid follicles.

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Immunostaining for CD3 indicated a positive reaction with heterogeneous distribution in the lung parenchyma. It was noticed an accumulation in the lamina propria of bronchioles (fig. 1a) and an abnormal distribution in the lymphoid follicles (germinal center) (fig. 1b).

CD20 expression was intense in the lymphoid follicles (fig. 1c) compare with CD5 immunoreaction which showed rare and weakly positive cells in the same area (fig. 1d). The reaction for CD15 was negative.

Bcl 2 positive reaction was restricted to the periphery of lymphoid follicles, respecting the normal distribution of this marker (fig. 1e). Immunostaining for Ki67 revealed a positive reaction in the germinal center of lymphoid follicles (fig. 1f).

Expression of CD68 was intense in the cells with macrophages morphology. Immunostaining with anti-mast cell tryptase antibody showed a high number of mast cells around the lymphoid follicles, in the connective tissue. Many mast cells were founded, concentrated in the immediate vicinity of the respiratory epithelium, in the lymph nodes from this area. In the lymph nodes which are not surrounded by epithelium, mast cells were disposed to the periphery of these, in a smaller number compare with previously situation. Only a few, isolated follicles presented mast cells in the central areas. The most of the nodules were situated in the vicinity of blood vessels. In this area was found a high number of mast cells with an oval shape, most of them partially degranulated (fig. 1g). Free mast cells granules were noticed among the collagen fibers, around vessels from the vicinity of nodules. The numerical distribution of mast cells was different from one node to another. The dimensions were relatively small. An extremely high number of mast cells were found in the interalveolar septa (fig. 1h).

Results and discussions

The diagnosis of delayed- type hypersensitivity was sustained in our case by immunohistochemical profile: CD3 positive with heterogeneous distribution in the lung parenchyma, CD20 intense positive in the lymphoid follicle, Bcl2 positive, with normal distribution in the lymphoid follicle, CD15 negative, CD68 positive, mast cell tryptase positive heterogeneous. An accurate differential diagnosis represents an important step for patient's evolution and prognosis. The differential diagnosis with other diseases which have the delayed type hypersensitivity as mechanism is important to make.

Enander et al, 1988 [7] studied the appearance of mononuclear cells, mast cells and mucus-producing cells in the lung and their linkage to the development of delayed hypersensitivity (DH) reactions. After in vivo treatment with the monoclonal GK1.5 (anti-L3T4) antibody resulting an inhibition of the DH reaction and a decrease number of mononuclear cells and mucus-producing cells, but not mast cells in the lung of sensitized and challenged mice. In our case, many mast cells were concentrated in the immediate vicinity of the respiratory epithelium, in the follicle from this area. In the follicles which are not surrounded by epithelium, mast cells were disposed to the periphery of these, in a smaller number compare with previously situation.

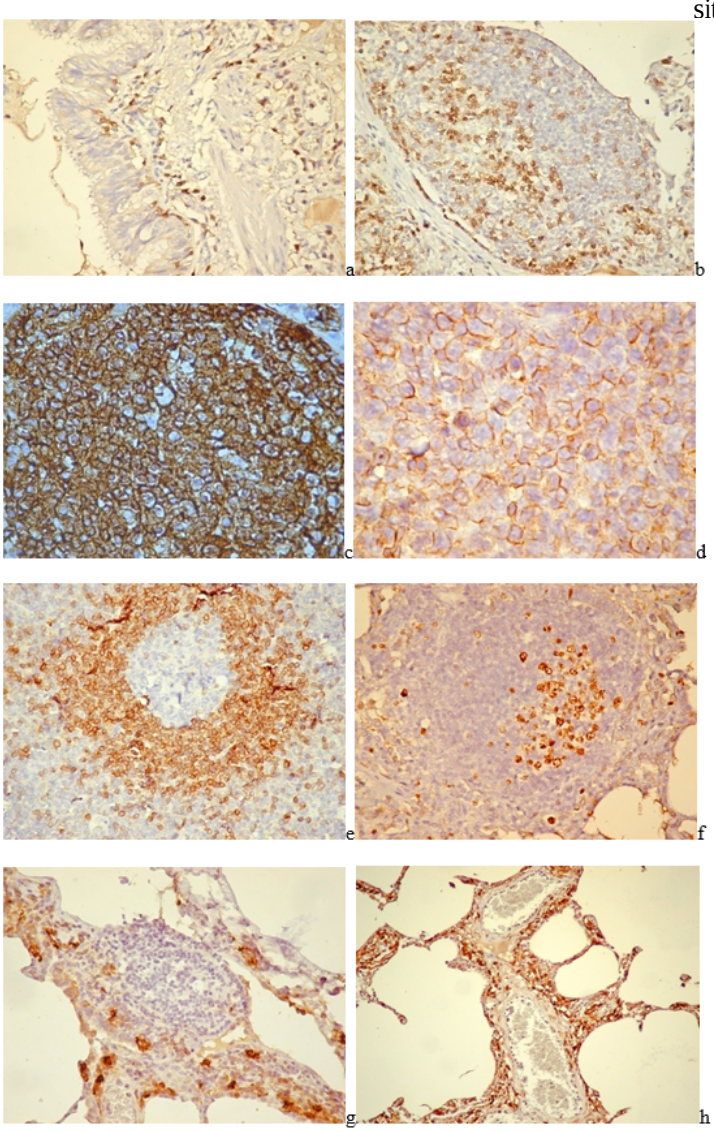

Fig.1a- Immunostaining for CD3. Heterogeneous distribution of CD3 in the lung parenchyma, with accumulation of positive cells in the lamina propria of bronchioles, X 100;
Fig.1b- Immunostaining for CD3. The abnormal distribution in the germinal center of the lymphoid follicles, X 100;
Fig.1c- Immunoexpression of CD20. An intense expression in the lymphoid follicles, X 400;
Fig.1d- CD5 immunoreaction. Rare and weakly positive cells in the lymphoid follicles, X 400;
Fig.1e- Immunoexpression of Bcl 2. The normal distribution, with reaction limited to the periphery of lymphoid follicles, X 100;
Fig.1f- Immunoexpression of Ki67. Positive reaction in the germinal center of lymphoid follicles, X 200;
Fig.1g- CD68 immunoreaction. Mast cells with an oval shape, most of them partially degranulated, X 200;
Fig.1h. CD68 immunoreaction. High number of mast cells situated in the interalveolar septa, X 100.

In the lung, hypersensitivity pneumonitis (HP) is a relatively rare and is characterized by the predominance of mononuclear inflammation of the lung interstitium, terminal bronchioles and alveoli. The histopathological specimens show interstitial inflammation accompanied by organizing pneumonia and multinucleate giant cell typical of hypersensitivity pneumonitis. The most significant clinical feature of HP is granuloma formation (absent to our patient), possibly progressing to lung fibrosis. Historically, HP has predominantly resulted from occupational exposures and therefore has a variety of names based on occupation or antigen association (farmer's lung) [8]. A combination of host and environmental factors should be considered as a requisite to developing this disease. Although the antigens differ widely, the clinical syndromes that results are very similar. HP occurs mainly in non-smokers, and clinically it may be in acute, subacute, or chronic forms.

It can be excluded another diseases with granuloma formation: TB (caseating granulomas, cavities with approximation of walls, granulation tissue, fibrosis and stelate scar), sarcoidosis (non-caseating epithelioid granulomas with tightly packed epithelioid cells, Langhans giant cells and lymphocytes (T cells), usually in interstitium adjacent to bronchioles and around and within vessel walls, pleura and connective tissue septa; necrotizing sarcoid granulomatosis: extensive, vascular, non-caseating sarcoid-like granulomas invading pulmonary arteries and veins with diffuse necrosis of lung parenchyma, Schaumann bodies, asteroid bodies).

Among the diseases that can be addressed in the differential diagnosis include chronic obstructive pulmonary disease (COPD). This is an inflammatory disease in which the cellular infiltrate is comprised primarily of CD81 /Tc1 and CD41 /Th1 lymphocytes and macrophages. This infiltrate, which persists long after cigarette smoking is ended, is diffusely distributed throughout the lung, including the small airways, submucosal glands, lung parenchyma, and pulmonary arteries. In addition, T cells, B cells, macrophages, and dendritic cells aggregate into organized lymphoid follicles in close proximity to the airways and within the lung parenchyma [9]. Compare with this, our case presented lymphoid follicles in the lung parenchyma and a high number of mast cells around blood vessels and in the interalveolar septa also.

Microscopic description of lymphoid interstitial pneumonia (LIP) included: lymphocytes with germinal centers, plasma cells, macrophages and epithelioid granulomas in lung interstitium, no effacement of alveolar architecture, no invasion of parietal pleura, although visceral pleura may have mild inflammation, late- diffuse interstitial fibrosis. Our case did not present ephiteloid granulomas, but its lung architecture showed alveoli irregular distension, massive accumulation of macrophages in the alveolar lumen, focally associated with edema. It was noticed a high number of intravascular and extravascular eosinophils without a significant fibrosis.

Immunophenotyping studies for lung non-Hodgkin lymphoma used antibodies to Ki-67, CD3, CD5, CD10, CD19, CD20, CD22, CD23, CD45 and CD79a selectively according to suspected subtype [10]. Our case presented CD3 positive in germinal centre of lymphoid follicle, CD20 intensely positive in the lymphoid follicle, CD 5 rare and weakly positive in lymphoid follicle, CD15 negative. These aspects excluded non-Hodgkin lymphoma diagnosis.

There are many forms of drug delayed hypersensitivity. From these, to the lungs have been described 2 cases of respiratory type-IV hypersensitivity reactions due to corticosteroids like a rare phenomenon. Constantinos, 2009 [11] presented a case of a patient who developed fever, arthralgias, myalgias, leukocytosis, and ARDS following a second infliximab infusion, after a 15-month drug holiday. Human antichimeric antibodies (HACA) were strongly positive, and no other etiology for acute respiratory distress syndrome (ARDS) was discovered. This may have represented an unusually severe delayed hypersensitivity reaction to infliximab. Our patient presented simphtomatology after professional dust exposure. In the literature, other cases with effects to the lungs were described by Riegert, 2002 [12]- a case of adult respiratory distress syndrome associated with infliximab therapy, Potenza, 2010 [13]- dysesthesia and laryngeal spasm developed 10 h after the sixth administration of oxaliplatin to a 46-year-old man with adenocarcinoma of the sigmoid colon.

Conclusions

Lung delayed type hypersensitivity diagnosis requires analysis of correlation between clinic, radiographic, physiologic and pathologic criteria.

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