

HISTIOCYTIC LESIONS

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The spectrum of histiocytic lesions that may present as pulmonary tumor or tumor-like lesion is wide and encompasses lesions of different etiologies including infectious, metabolic, environmental, and of unknown histogenesis among others. This section will cover lesions that may present either as a pulmonary mass or nodules. However, even with this sub-grouping, it is impossible to cover the wide spectrum of pathological conditions that may be present in that form. For instance, it is well known that systemic conditions such as storage diseases like Fabry's disease infantile GM1-Gangliosidosis, Gaucher's disease, and Niemann-Pick disease may involve the lung. However, it is very unlikely that in those conditions a previous diagnosis has been established and the lung is involved secondarily. In addition, other systemic condition such as Whipple disease may in some cases involved the lung. Although those previously mentioned conditions may be part of the spectrum of histiocytic lesions, they will not be covered in this sections as they represent systemic diseases with only secondary pulmonary involvement. Therefore, only a selected group of lesions will be covered in this section, which may share similar histopathologic and immunohistochemical features. These include:

- Langerhans cell histiocytosis
- Erdheim-Chester disease
- Rosai-Dorfman disease

- Juvenile Xanthogranuloma
- Crystal storing histiocytosis
- Malacoplakia

Pulmonary Langerhans Cell Histiocytosis (PLCH)

PLCH has also been referred as primary pulmonary histiocytosis X, eosinophilic granuloma of the lung, and Langerhans cell granulomatosis. This type of histiocytosis may involve the lung in two different patterns either as a solitary lung process or secondarily as part of a systemic process. It is well known that Langerhans' cell histiocytosis may present in adults as either single organ involvement or as a multisystem disease. This section will cover the single organ involvement, namely that occurring in the pulmonary region.

Although numerous reviews and case series have been reported, the occurrence of PLCH is difficult to determine and there is not hard data on the prevalence of it. In a study of 502 patients who had a lung biopsy, 17 patients (3.4%) were diagnosed with PLCH. However, others have estimated that about 25% of the cases are initially identified during routine chest radiographs, which may disclose pulmonary abnormalities. Although the exact pathogenesis of PLCH is unknown, Soler et al suggested an uncontrolled immune reaction. Nevertheless, it is important to highlight that clonality has been determined in cases of Langerhans' cell histiocytosis. Willam et al studied 10 cases of langerhans cell histiocytosis -none of them in the lung using human androgen receptor assay (HUMARA) and identify clonality in 9 of 10 cases studied. Yu et al in a different study also documented clonality. Yousem et al using also HUMARA studied 24

nodules of 13 patients, finding that 29% show clonality and 71% were non-clonal. Thus, the authors concluded by stating that PLCH appears primarily a reactive process.

Clinical Features

PLCH occur more often in adult patients in their third or fourth decade of life. However, PLCH has also been described in children. Racially, the process is more common in the white than in the black population. Regarding gender, different studies have determined equal incidence in both genders, higher incidence in men, and higher incidence in women. However, one consistent association has been with cigarette smoking, which can be seen in about 80% of patients. Patients with PLCH may present with respiratory symptoms including cough, chest pain, dyspnea, hemoptysis, and/or pneumothorax. However, about 20% of the patients may be completely asymptomatic and the process is first evident during a routine chest radiograph. Radiologically, the characteristic feature is that of a reticulonodular bilateral infiltrate. However, it has also been stated that in some cases the radiographic findings may be non-specific. Although the diagnosis is more often made with an open lung biopsy, in some studies, a few cases have been diagnosed with a transbronchial biopsy.

PLCH has also been associated with neoplastic conditions including non-Hodgkin's lymphoma, Hodgkin's lymphoma, and carcinoma. Therefore, close clinical, radiological, and histopathological correlation is required in order to properly address such associations.

Macroscopic Features

In open lung biopsies or wedge resections, PLCH shows multiple parenchyma nodules of different sizes, which may vary from under 1 cm to more than 3 cm in

diameter. These nodules are whitish, firm, well circumscribed but not encapsulated. Areas of necrosis and/or hemorrhage are not common but may be seen.

Histopathological Features

The low power magnification is that of different parenchymal nodules of different sizes obliterating normal lung parenchyma. These nodules have a stellate shape with the so-called “medusa’s head,” however, some nodules do not show this features but rather have a round contour. Necrosis and/or cavitations may be seen in about 20-25% of the cases. High power magnification show the presence of a proliferation of histiocytes admixed with inflammatory cells, which in the majority of cases will characteristically show the presence of numerous eosinophils. However, some nodules show more fibrotic changes and not marked inflammatory infiltrate with only scattered eosinophils. The presence of eosinophils although helpful in the diagnosis is not required. The histiocytes characteristically show indented or grooving nuclei. This process may also extend into the alveolar wall without forming a nodule, the same as it may also involved blood vessels, and airway. Also important is to mention, the changes that may be observed in the non-involved lung parenchyma. These changes may include desquamative interstitial pneumonitis (DIP)-like reaction, which consist in the accumulation of pigmented laden macrophages within alveolar spaces with mild interstitial fibrosis.

Immunohistochemically, PLCH shows positive staining for S-100 protein, CD-1a, HLA-DR, langerin, and E-cadherin. Ultrastructurally, langerhans cell show the typical Birbeck granules or racketoid, or rod-shaped organelles characteristic of Langerhans cell histiocytosis.

Differential Diagnosis

Although PLCH is rather a straight forward diagnosis, in some cases, the characteristic features are not readily visible and other conditions may be considered including Erdheim-Chester disease, malignant lymphoma, and/or eosinophilic pneumonia. In any of these settings, the use of immunohistochemical studies and the correlation with the radiographic findings may help in arriving at a correct interpretation.

Treatment and Prognosis

Several approaches may be included in the treatment of PLCH including cessation of smoking, steroids, chemotherapy, or lung transplantation. In this latter form of treatment usually reserved to patients with severe compromised lung function, it is important to keep in mind that recurrences of PLCH have been documented in the transplanted lung. Each one of these approaches will depend largely on individual basis and on the respiratory function of the individual. It appears that smoking cessation is very important in the treatment of these patients. Although many studies have suggested a good prognosis, some patients go on to develop respiratory insufficiency and died as a consequence of PLCH. Vassallo et al reviewed 102 adults with PLCH who were followed-up for a period of 0 to 23-years (median: 4 years), in this study the authors found 33 deaths, 15 of those deaths were attributed to respiratory failure with an overall median survival of 12.5-years. The authors also found 6 patients malignant lymphoproliferative disorders and 5 patients with lung carcinoma.. The authors concluded that the survival of adults with PLCH is shorter than that in the general population.

Erdheim-Chester Disease

This type of histiocytosis is rare and only a few series of cases have been presented in the literature. William Chester and Jacob Erdheim described this condition in 1930 as a form of lipoid granulomatosis different from other lipidosis. The authors described two autopsy cases in which the process was present in bone and viscera. Jaffe in 1973 reported an additional case and coined the term Erdheim-Chester disease.

Clinical Features

The clinical presentation of patients with Erdheim-Chester disease varies considerably depending on the organs involved. Even though, the emphasis here will be on pulmonary symptoms, it is important to recognize that patients with this condition although may present with pulmonary symptoms, that does not necessarily mean that the lung is the only site involved, and a search for other sites is highly recommended. Therefore, it is important to keep in mind that Erdheim-Chester is usually a multisystem process that may involve different anatomic sites. One of the most common presentations is that of skeletal abnormalities including expansile lesions of the ribs, symmetrical patchy sclerosis and thickening of metaphyses of long tubular bones and/or patchy sclerosis of the calcaneus. Other extra-skeletal symptoms may include dyspnea, pulmonary infiltrates and pleural effusion, pulmonary fibrosis, congenital megacalices, hydronephrosis, hydroureter, chronic lipogranulomatous pyelonephritis, retroperitoneal xanthogranulomas, ophthalmic abnormalities, and hyperlipidemia.. the most indicated way to arrive at a more precise diagnosis is by performing an open lung biopsy in cases with pulmonary symptoms.

Histopathological Features

The histopathologic features of this process in the lung are rather characteristic. The low power view is that of a process involving pleura and pulmonary septum. In some cases the involvement is more extensive with pleural, septal, and parenchymal involvement. The histiocytic proliferation composed of small to medium size histiocytes with foamy or finely granular cytoplasm and their nuclei do not show the grooving of the nucleus as in cases of PLCH. Granulomatous changes are not characteristic of this process. The histiocytic infiltrate usually involves the pleura and pulmonary septum while the lung parenchyma appears to have changes more in keeping with interstitial lung disease and/or emphysematous changes. The histiocytic proliferation may also show a discrete inflammatory infiltrate composed of lymphocytes and plasma cells but rarely show marked inflammatory component and eosinophils when present are not in increase number.

Immunohistochemical studies in the histiocytic proliferation show positive staining for CD-68 (Kp-1) and factor XIIIa with while CD-1a is negative. On the other hand, S-100 protein may show variable staining and reported cases of negative and positive staining has been documented.

Treatment and Prognosis

There is not specific treatment for this condition and different approaches have been attempted including corticosteroids, interferon- α 2a, surgical debulking, and/or chemotherapy; however, the prognosis for patients with Erdheim-Chester disease and pulmonary involvement is rather poor as those patients follow a fatal course with respiratory failure.

Rosai-Dorfman Disease

Rosai-Dorfman disease also known as sinus histiocytosis with massive lymphadenopathy (SHML) is a process of ubiquitous distribution as it has been described essentially everywhere in the body. Although the etiology of this condition is still unknown, different theories to explain its occurrence have been stated including an immunologic response or an infectious origin. Paulli et al evaluated two cases in which the authors use HUMARA finding that the histiocytic proliferation was polyclonal. The process as originally described is more often encountered in young adults and the most common anatomic site is in lymph nodes. It has been stated that Rosai-Dorfman disease may involve extra-nodal site in about 20% of the cases. However, the respiratory system, namely the lung and pleura are among the most unusual sites of occurrence. In addition, in some of the cases described involving lung parenchyma, the lung has become involved in addition to other sites, namely lymph nodes. Thus, the presence of this condition as occurring solely and primarily in the lung parenchyma and/or pleura is exceedingly rare. When this condition affects the lung parenchyma, the patient may present with an intrapulmonary mass, which may be indistinguishable clinically or radiologically from other neoplastic process. Therefore, the best approach to arrive at a more specific diagnosis is tissue diagnosis. However

Histopathological Features

The microscopic features of Rosai-Dorfman disease in the lung are similar to those described when this process affects lymph nodes. The main histologic hallmark of the process is the proliferation of large histiocytes, which may have one or more nuclei and ample pale cytoplasm. Some of these lymphocytes may show the presence of lymphophagocytosis or emperipolesis; however such finding may not be readily apparent

in some cases. In addition, the histiocytic proliferation is usually in the background of a prominent inflammatory response composed predominantly of plasma cell and lymphocytes. In general, the two most important cellular components of Rosai-Dorfman disease is the presence of large histiocytes and plasma cells. The pulmonary parenchyma is clearly replaced by the process and the adjacent uninvolved lung parenchyma may show features of interstitial lung disease.

Immunohistochemical studies may of help in the diagnosis of this condition as the histiocytes show positive staining for S-100 protein, CD68, CD15, CD163, and α 1-antichymotrypsin, while the histiocytes are negative for CD1a and factor Xiiia.

Treatment and Prognosis

There is not a specific treatment for this condition and the prognosis may be related to the extent of the process at the time of diagnosis. In more limited cases, surgical resection of the tumor mass may be accomplished follow by observation; while in cases with more systemic involvement surgical resection followed by medical therapy could be attempted. However, the use of chemotherapy has not shown meaningful benefits. Foucar et al followed 238 patients and found that 21 patients had died, four due to this process, 13 with the process, and four without the process. On the other hand, 49 patients were alive without disease after 1 year while 36 had persistent disease. Whether lung involvement plays a role in the survival rate of these patients is difficult to determine due to the rare occurrence of this process in the lung.

Pulmonary Juvenile Xanthogranuloma (PJXG)

PJXG is a grouped among the non-largerhans cell histiocytosis. This is an unusual condition of rare occurrence in the lung parenchyma and only a few cases have

been reported in the literature. Contrary to Langerhans cell histiocytosis in which the cell of origin is basically known, in JXG the putative cell of origin has been speculated to be the dermal dendrocyte; however, this theory would not explain those lesions that occur primarily in deep seated tissues or in viscera. Therefore, some authors have speculated on the possibility of a plasmacytoid monocyte as the cell of origin. Nevertheless, such theories remain speculative.

PJXG is more common in children and young adults and may affect the lung only rarely. When the lung is involved, the lesion may be bilateral, unilateral, multiple, or single. Rarely the lesion would be single and as the presenting symptom, although it has been reported in sporadic cases. Often, the patients have dermal involvement and/or involvement of other viscera.

Pathological Features

Grossly, this lesion may present as a solitary lung nodule or mass of varying size, which may range from under 1 cm to more than 3 cm in greatest dimension. The lesions are soft and yellowish well demarcated but not encapsulated.

Histologically, the low power view is that of a well-circumscribed but not encapsulated mass destroying lung parenchyma. Higher magnification shows a proliferation of histiocytes, which may range from small to medium size with or without prominent nuclei. The histiocytic proliferation may be accompanied by an inflammatory infiltrate composed of lymphocytes and plasma cells. In some areas nodular collections of lymphocytes may be seen. Also in focal areas, admixed with the histiocytic proliferation, scattered multinucleated giant cells may be seen. These giant cells are

difficult to find and in many cases they are absent. Nuclear atypia, mitotic activity, necrosis and/or hemorrhage are not common in this process.

Immunohistochemical studies of dermal JXG have shown positive staining of histiocytes for CD68, factor XIIIa, HLA-DR, LCA, CD4, and S-100 protein. However, the tumor is negative for CD1a, CD3, CD21, CD34, and CD35. In addition, ultrastructural studies are negative for the presence of Birbeck granules.

Treatment and Prognosis

The rarity of this lesion in the lung parenchyma preclude from unequivocally stating whether it has an impact in the survival of these patients. Most likely, it is the extent of the disease at the time of diagnosis what determines the outcome of these patients. Surgical resection of the pulmonary lesions appears to be a logical approach in cases in which such procedure can be accomplished.

Crystal Storing Histiocytoma or Histiocytosis

This is an unusual process that can present with or without an association with lymphoproliferative disorders. The most common lymphoproliferative process involved is multiple myeloma. Crystal storing histiocytoma has been suggested as a term when this process occurs without any association with a lymphoproliferative disorder. It is believed that this process is reactive in nature in contrast to the one associated with a lymphoproliferative disorder. On the other hand, if the process is associated with a lymphoproliferative disorder, the more generic name of crystal storing histiocytosis should be used. This type of process has been identified in several organ systems including the gastrointestinal, genitourinary, hematopoietic and respiratory system. Three different storing components have been identified in this process: 1) crystallized

immunoglobulins; 2) phagocytosed clofazimine in patients receiving treatment for leprosy; and 3) Charcot-leyden crystals. However, regardless of the material accumulated the basic histology is similar, namely the presence of a histiocytic proliferation.

Pathologic Features

At low magnification, in crystal storing histiocytosis the lung parenchyma appears to keep its basic architecture; however, the alveoli appear filled with an eosinophilic material that in some areas appears to spill into the interstitium given the appearance of a fibrinous type of exudates. At higher magnification, the material filling the alveoli is characterized by the presence of a histiocytic proliferation composed of larger histiocytes with ample cytoplasm and small round nuclei. The cytoplasm of the histiocytes is filled with crystalloid material representing crystallized immunoglobulin. On the other hand, crystal-storing histiocytoma presents as a pulmonary mass or nodule replacing lung parenchyma. In some cases the histiocytic proliferation gives the appearance of “muscle” proliferation as seen in cases of rhabdomyomas. In some cases the histiocytes appear to contain a rather granular type of material non-crystallized immunoglobulin.

Immunohistochemical studies may be of aid to determine the presence of a histiocytic proliferation as the cells show positive staining for CD68 and also may show a monoclonal arrangement of immunoglobulin by using kappa or lambda stains. The histiocytes are negative for CD1a, and Factor XIIIa. Electron microscopy will ultimately determine the type of crystal material present in the cytoplasm of these histiocytes.

Treatment and Prognosis

Surgical resection for the tumor-like lesion present in the lung parenchyma appears to be the treatment of choice. However, recurrences have been documented. Nevertheless, the prognosis of this process will be determined by the associated condition present. It is imperative that in cases limited to the pulmonary parenchyma and without an obvious lymphoproliferative process, a complete clinical evaluation should be undertaken to make sure that the patient does not have an occult neoplasm.

Pulmonary Malakoplakia

This process is not a bona fide histiocytic process but rather an infectious process, which may elicit a histiocytic response. Therefore, it will be discussed among this group of lesions of histiocytic nature.

Malakoplakia is a process of ubiquitous distribution that has been described in many organ systems including the genitourinary, central nervous, and gastrointestinal system. Although some authors have suggested that the process is secondary to an infection with E. Coli, in the lung, it has been associated commonly with the Acquired Immunodeficiency syndrome (AIDS) or in patients with other immunosuppressive states and often in association with other agents including Rhodococcus equi and Pasteurella. Clinical and radiological features of patients with pulmonary malakoplakia are rather non-specific. Tissue is required for final diagnosis.

Pathologic Features

Malacopkia in the lung can present as an endobronchial nodule or as an intra-parenchymal pulmonary mass with destruction of the lung parenchyma and necrosis indistinguishable from another pulmonary neoplasm.

The lung parenchyma may have one or more pulmonary nodules of different sizes. The lung parenchyma may show the presence of a histiocytic proliferation admixed with plasma cells and scattered Michaelis-Gutman bodies, which is the pathognomonic feature of malakoplakia. However, in some instances, malakoplakia in the lung may have the low power appearance of bronchiolitis obliterans and organizing pneumonia with a proliferation of spindle cell fibroblastic proliferation admixed with lymphocytes and plasma cells and numerous Michaelis-Gutman bodies. This type of pattern may be easily confused with BOOP or inflammatory pseudotumor of the lung. The use of special histochemical stains for iron or Von Kossa can be helpful in the identification of the Michaelis-Gutman bodies. Ultrastructural studies of Michaelis-Gutman bodies may show the presence of fingerprint-like pattern in some cases of malakoplakia.

Treatment and Prognosis

If the lesion is forming a pulmonary nodule complete surgical resection is curative. If there is any particular infection associated with this process, then treatment for that specific infection should be started. Although this process is benign, the underlying condition is the one that will determine the outcome in these patients.

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