Article is available online at http://www.webio.hu/por/2002/8/4/0280

CASE REPORT

Pulmonary Lymphomatoid Granulomatosis Evolving to Large Cell Lymphoma in the Skin

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Lymphomatoid granulomatosis is an angiodestructive, angioinvasive lymphoproliferative disorder. It involves most frequently lungs, central nervous system and skin. Recent studies indicate that lymphomatoid granulomatosis is an Epstein-Barr virus associated B cell disorder with a background of reactive T lymphocytes. In a 49 year old woman presenting with fever, malaise and pulmonary masses the diagnosis of lymphomatoid granulomatosis was established histologically by open lung biopsy. Following the initial diagnosis the patient was found to have gastric and skin involvement. The skin lesion was diagnosed as diffuse large B-cell lymphoma. (Pathology Oncology Research Vol 8, No 4, 280–282)

Keywords: Lymphomatoid granulomatosis, Epstein-Barr virus, large cell lymphoma, angiocentric lymphoma

Introduction

Lymphomatoid granulomatosis (Lyg) is an angiocentric, angiodestructive neoplastic proliferation of B and T lymphocytes commonly involving the lungs, skin, central nervous system (CNS) and the bone marrow.[1,2] Epstein-Barr virus (EBV) is commonly detected in the lesional cells.[3,4] Even though the majority of lymphocytes are of T cell origin, the neoplastic clone is believed to arise from B lymphocytes. This issue is still controversial since in some cases there is also a clonal proliferation of T cells, detected by molecular methods such as T-gamma receptor rearrangement studies performed by PCR. These lesions used to be classified as angiocentric lymphomas. However, despite their angiocentricity, these lymphomas should be distinguished from the nasal type T/NK lymphomas that are also associated with EBV.[3,4]

Case report

A 49 year old woman presented with complaints of fatigue, abdominal pain, productive cough and weight loss for a one year duration. She claimed to have lost 20 kgs during this period. On physical examination, focal depigmented patches on the skin and pulmonary rales were noted as well as hepatosplenomegaly. Chest X-ray revealed bilateral hilar infiltrates as well as peripheral densities of left lung and right pleural effusion. By ultrasonographic exploration, multiple lymphadenopthies in the axillary region were detected. Chest CT revealed multiple pulmonary nodules largest of which measuring 7 cm. in diameter *(Figure 1.)*. Patient underwent bronchoscopic examination which was negative for malignancy. This procedure was followed by open biopsy of the lung which yielded the diagnostic specimen. Microscopic examination of the lung tissue sections revealed an organising pneumonia pattern in most sections. However there were occasional nodular areas which revealed a dense collection of lymphocytes some of which appeared enlarged and atypical. Focally these infiltrates appeared angiocentric, with no evident destruction of the vessel wall *(Figure 2.)*. Immunohistochemical analysis of the infiltrates revealed a predominantly T cell infiltrate. However, there were occasional clusters of large and atypical lymphocytes that stained for B cell markers such as CD20 and CD79a. There was no staining for CD30 and scattered staining for NK-like marker among the mature appearing T lymphocytes. Based on the clinical and pathological findings a diagnosis of Lyg was rendered. Following the initial diagnosis the patient was treated with Fludarabine. Two months following the initial diagnosis a stomach biopsy was performed due to dyspeptic symptoms. The biopsy revealed a diffuse infiltrate of intermediate and large

Received: Oct 29, 2002; *accepted:* Dec 10, 2002

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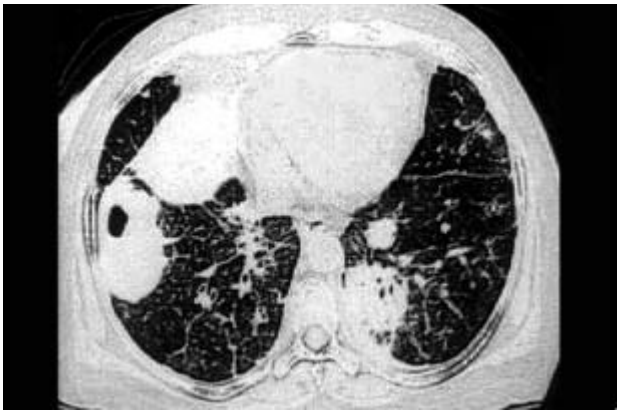

Figure 1. Chest CT, pulmonary nodules largest of which measuring 7 cm

lymphocytes spanning the entire submucosa causing focal ulceration of the mucosa. Immunohistochemical studies revealed a predominantly B cell infiltrate. These findings were reported as consistent with involvement by Lyg. The patient also complained of skin lesions which appeared papular and pustular. The skin biopsy revealed a deep, diffuse and perivascular and periadnexial large and atypical lymphocytic infiltrate with no epidermotropism. Immunohistochemical studies revealed that these lymphocytes were entirely B cells. The case was diagnosed as large B cell lymphoma involving the skin. The case was unresponsive to chemotherapy and died within 6 months following the initial diagnosis.

Discussion

Lyg is a rare systemic lymphoproliferative disorder commonly involving the lungs. Lyg is most commonly diagnosed between 4th and 6th decades.[5] Patients usually present with fever, cough, hemoptysis. Typical radiological features are multiple parenchymal nodules mimicking metastatic tumors. Pneumonic consolidation and interstitial infiltrates can also be the only radiological manifestations of Lyg. Histologically, Lyg has an angiocentric and angioinvasive pattern.[6] The infiltrate is usually polymorphous. The nodules usually consist of pleomorphic atypical lymphocytes. The lymphocytes are predominantly of T cell origin. The rare pleomorphic atypical cells usually express B cell markers such as CD20, CD79 etc.[7,8] In our case most sections of the pulmonary tissue were consistent with organising pneumonia. Striking features that differed from an organising pneumonia pattern were the angiocentric and angiodestructive lymphocytes and the presence of lymphoid nodules containing large atypical lymphocytes. Skin involvement by Lyg usually consists of a predominantly T cell infiltrate with a perivascular pattern.[1-3] The angiocentricity and angiodestructiveness of the infiltrates of Lyg could be due to the chemokines released by the T cells. EBV may be the culprit in stimulating the lymphocytes release these chemokines.[2] Until recently, Lyg has been considered a T cell lymphoproliferative disorder and classified as such. Recent studies however, demonstrated the presence of a clonal atypical B cell population which is infected by EBV. All the T cell infiltrates in the lesion are considered to be reactive.[3,4] Immunosuppression may be an underlying factor in the development of Lyg since Lyg has been associated with AIDS, Wiskott-Aldrich syndrome, and transplant patients.[2] Pulmonary lesions such as histoplasmosis, tuberculosis, abcess formation and hydatid cysts are among the lesions considered in the differential diagnosis based on the radiological findings. In addition Wegener‘s granulomatosis and nasal type T/NK lymphomas should also be considered in the differential diagnosis. There are a small number of T cells in this lesion, but most of the cells are plasmacytoid B cells. Hodgkin‘s lymphoma may also be part of the differential diagnosis. But the involvment of the lungs without hilar and mediastinal lymphadenopathy is detected in Lyg. Besides, there are no classical Reed-Sternberg cells in Lyg and the large B cells are CD15 negative. The distinction can be made from Churg-Strauss vasculitis by the lack of tissue eosinophilia. So far, there is no optimal treatment for Lyg, but immunosuppressive treatment, especially aggressive and combined chemotherapy are applied.[6] There have also been successful results with the application of interferon- 2b.[3] Most of the patients are resistant to radiotherapy and die in one or two years. Death usually results from pulmonary complications, CNS involvement or lymphoma growth. It is said that, if the cell population is composed of small lymphocytes the prognosis is better. Absence of systemic involvement, normal total blood count and biochemical values, and existence of a small number of atypical cells by histopathologic examination are all indicative of a good prognosis in short term.[5] The younger age of the patient, or the existence of hepatosplenomegaly are poor prognostic factors.[2]

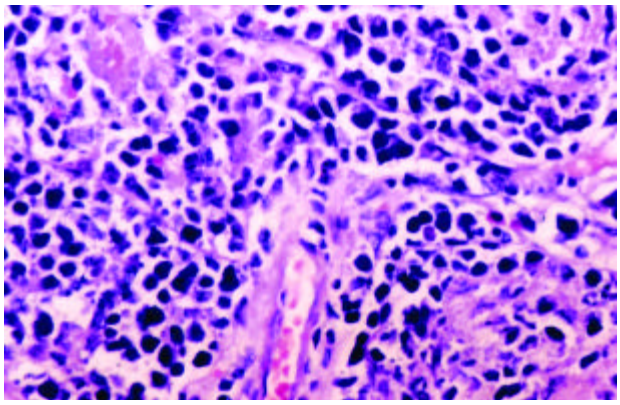

Figure 2. Lymphomatoid granulomatosis, angiocentric, enlarged and atypical lymphocytes. HE x200

Skin involvement by Lyg is common. However, usually there is a pleomorphic infiltrate mimicking the pulmonary lesions of Lyg. Diffuse large cell pattern of involvement is very rare. In a series of 20 cases of cutaneous involvement of Lyg, only one case with diffuse large cell pattern was described.[9] This case was also fatal like ours. We did not perform molecular analysis of the pulmonary samples and the skin and stomach samples. However, since there was very short duration between pulmonary and cutaneous presentations and since Lyg is known to involve skin frequently, it is safe to assume that the lesions represent systemic spread of Lyg. Recently there was a case report of Lyg presenting as diffuse large cell lymphoma in a transplant patient.[10]

We believe our case represents a rare occurrence of progression to diffuse large cell lymphoma in a patient with classical type Lyg. We also think that administration of fludarabine, which is known to deplete the bone marrow cells and the lymphocytes, might have caused an immunosuppressive condition and contributed to the progression and fatality of the patient.

In conclusion, Lyg is a rarely observed and sometimes aggressive lesion which may be confused with various lesions. It must be kept in mind in the differential diagnosis of lesions that show multifocal involvement in the lungs. An increase in the proportion of the large atypical lymphocytes seems to be a bad prognostic factor.

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References

1. *Patchefsky AS:* Nonneoplastic pulmonary disease. In: Sternberg SS (ed). Diagnostic surgical pathology, third ed. Philadelphia: Lippincott Williams&Wilkins pp 1035-1037, 1999
2. *Jaffe ES, Wilson WH:* Lymphomatoid granulomatosis: pathogenesis, pathology and clinical implications. Cancer Surv 30: 233-247, 1997
3. *Wilson WH, Kingma D, Raffeld M, et al:* Association of lymphomatoid granulomatosis with Epstein-Barr viral infection of B lymphocytes and response to interferon-2b. Blood 87: 4531-4537, 1996
4. *Kingma D, Fishback N, Wallberg K, et al:* Pulmonary lymphomatoid granulomatosis. Evidence for a proliferation of Epstein-Barr virus infected B-lymphocytes with a prominent T-cell component and vasculitis. Am J Surg Pathol 18: 753-764, 1994
5. *Karnak İ, Çiftçi AO, Talim B, et al:* Pulmonary lymphomatoid granulomatosis in a 4 year old. J Pediatr Surg 34: 1033-1035, 1999
6. *Lipford EH, Margolick JB Jr, Longo DL, et al:* Angiocentric immunoproliferative lesions: a clinicopathologic spectrum of post-thymic T-cell proliferations. Blood 72: 1674-1681, 1988
7. *Guinee DG, Perkins SL, Travis WD, et al:* Proliferation and cellular phenotype in lymphomatoid granulomatosis. Implications of a higher proliferation index in B cells. Am J Surg Pathol 22: 1093-1100, 1998
8. *Taniere Ph, Thivolet-Bejui F, Vitrey D, et al:* Lymphomatoid granulomatosis- a report on four cases: evidence for B phenotype of the tumoral cells. Eur Respir J 12: 102-106, 1998
9. *Beaty MW, Toro J, Sorbora L, et al:* Cutaneous lymphomatoid granulomatosis: correlation of clinical and biologic features. Am J Surg Pathol 25: 1111-1121, 2001
10. Saxena A, Dyker KM, Angel S, et al: Posttransplant diffuse large B-cell lymphoma of "Lymphomatoid Granulomatosis" type. Virch Arch 441:622-628, 2002