Lymphomatoid granulomatosis in one patient with newly diagnosed HIV infection and Kaposi’s sarcoma: a case report and literature review

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Abstract
Lymphomatoid granulomatosis is a very rare B cell lymphoproliferative disease associated with Epstein–Barr virus infection. It is related to states of immunosuppression and affects the lung in more than 90% of cases, forcing the clinician to establish a differential diagnosis with other diseases such as infections, Wegener’s granulomatosis, lymphoma, or lung metastases. There is no standard treatment for this disease. In this paper, we describe a rare case of a patient with grade 3 lymphomatoid granulomatosis with newly diagnosed HIV infection who started antiretroviral treatment with a gradual improvement of the lesions.

Keywords Lymphomatoid granulomatosis · Lung nodes · Epstein–Barr virus · Lymphoproliferative syndrome

Introduction

The World Health Organization (WHO) defines lymphomatoid granulomatosis (LYG) as an angiocentric and angiodestructive lymphoproliferative disease involving extranodal sites, composed of B cells positive for Epstein–Barr virus (EBV) and admixed with reactive T cells. This rare disease was previously described as polymorphic reticulosis, angiocentric immunoproliferative lesion, malignant angiitis, malignant granulomatosis, and angiocentric lymphoma. While most patients with LYG do not have a history of overt immunodeficiency, the disorder is more commonly diagnosed in patients with immunodeficiency and predisposing conditions include Wiskott-Aldrich syndrome, human immunodeficiency virus infection (HIV), and allogeneic organ transplantation [1, 2].

Case presentation

A 29-year-old man, with a recent diagnosis of HIV and skin lesions suggestive of Kaposi’s sarcoma (KS), was referred to the National Cancer Institute in Mexico City. A complete diagnostic protocol was done to rule out opportunistic infections, his CD4 cell count was 170 cell/mm³. He complained of weight loss, cough, exertional dyspnea, and moderate headache. The physical examination revealed skin lesions in the left malar region, left ear, right arm, hypogastrium, and right foot of 1 cm each, suggestive of KS. Endoscopy and colonoscopy revealed duodenal and colonic KS, human herpes simplex 8 related Kaposi’s sarcoma (HHV8) viral load was 730 copies/mL. Chest CT scan, identified two subpleural nodular images, one of 15 mm, located in the upper segment of the right lower lobe, with a soft tissue density, and the other in the left lung base of 21 mm (Fig. 1). CT scan–guided biopsy was performed with a pathology report of grade 3 lymphomatoid granulomatosis; the immunohistochemistry was positive for CD20, CD79a, BCL-6, MUM-1, C-MYC, and CD30, in situ hybridization for EBV-encoded small RNA (EBER-ISH) (>50 for high-power field) in neoplastic cells; positive for CD3, CD8, and CD4 in T reactive lymphocytes, CD 15 negative, CD68 positive in histiocytes, CD138 positive in plasmatic cells, and Ki67 of 40% (Fig. 2). Highly active antiretroviral therapy (HAART) with bictegravir, emtricitabine, and tenofovir was initiated. In follow-up, the patient complained...
Fig. 1 Axial window computerized axial tomography—lung; pulmonary nodules identified with yellow arrows and axial window computerized tomography—lung, images from PET-CT; pulmonary nodule absent, small size in the second image in bases identified with yellow arrows.

Fig. 2   a, b, c H/E staining, 4x/0.10 y 40X/0.65, needle lung biopsy made up of atypical large, pleomorphic cells are observed on inflammatory background with areas of necrosis and angioinvasion. d IHQ-CD3, 10x/0.25. Positive in reactive T lymphocytes (e, f, g). IHQ-CD20, CD79A, CD30: positive in neoplastic cells. h IHQ-KI67, 40X/0.65. Positive 40%. i In situ hybridization, EBER-ISH, 40X/0.65. Positive in neoplastic cells, more than 50 cells/high-power field.
of right posterior chest pain and an increase of the headache episodes. Magnetic resonance imaging (MRI) of the brain was performed identifying hyper-intense nodular images located in white matter and periventricular only assessed in FLAIR and T2 sequence, without enhancement after the application of contrast medium, or restriction in diffusion, described as nonspecific leukoaraiosis, and nonspecific meningeal reinforcement; the lumbar puncture was negative for infiltration. High blood pressure was documented and antihypertensive treatment was started. A control CT scan chest showed an increase in the number and size of the pulmonary nodules. Anti-CD20 therapy deferred because of the COVID-19 pandemic. In the following months, the patient had a decrease in size and later resolution of the skin lesions of KS and had an improvement of the cough and dyspnea, HIV and HHV8 viral load were undetectable, and the CD4 count normalized only with retroviral treatment. A PET-CT count normalized only with retroviral treatment. A PET-CT scan was performed finding cervical lymph nodes with an inflammatory reactive appearance, and a decrease in the size of the pulmonary nodules, with a low metabolism (Fig. 1).

Discussion

LYG is an angiocentric and angiodestructive lymphoproliferative disease composed of EVB-positive large atypical B cell, a prominent population of small reactive T cells, and necrosis; almost all cases involve the lung (multiple pulmonary nodules); the skin is involved in nearly half of cases (dermal and subcutaneous nodules show similar features to the lung but may show nonspecific plaque-like dermal infiltrate); CNS and kidney are also frequently involved. High-grade lesions with a preponderance of large atypical B cells are considered diffuse large B cell lymphoma [2–4].

The EBV-positive B cells usually express CD20, are variably positive for CD30, but are negative for CD15. LMP1 maybe positive. EBNA2 is frequently positive. In rare cases, monotypic cytoplasmic immunoglobulin expression may be seen, particularly in cells showing plasmacytoid differentiation. The background lymphocytes are CD3+ T cells, with CD4+ cells more frequent than CD8+ cells.

The grading of LYG relates to the proportion of EBV-positive B cells relative to the reactive lymphocyte background:

Grade 1 lesions contain a polymorphous lymphoid infiltrate without cytological atypia. Large transformed lymphoid cells are absent or rare and are better appreciated by immunohistochemistry. When present, necrosis is usually focal. By EBER, only infrequent EBV-positive cells are identified (< 5 per high-power field).

Grade 2 lesions contain occasional large lymphoid cells or immunoblasts in a polymorphous background. Small clusters can be seen, in particular with CD20 staining. Necrosis is more commonly seen. EBV-positive cells are easily identified by EBER-ISH, typically numbering 5–20 per high-power field. Variation in the number and distribution of EBV-positive cells can be seen within a nodule or among nodules, and occasionally as many as 50 EBV-positive cells per high-power field can be observed.

Grade 3 lesions still show an inflammatory background but contain large atypical B cells that are readily identified by CD20 and can form larger aggregates. Markedly pleomorphic and Hodgkin-like cells are often present, and necrosis is usually extensive. By EBER-ISH, EBV-positive cells are extremely numerous (> 50 per high-power field), and focally may form small confluent sheets [1, 5–7].

In this case, needle lung biopsy revealed atypical large, pleomorphic EBV-positive cells (> 50 per high-power field) on an inflammatory background with areas of necrosis and angioinvasion.

Differential diagnosis of LYG includes post-transplant lymphoproliferative disorder, Wegener granulomatosis, extranodal NK/T cell lymphoma, and Hodgkin lymphoma, among others (Table 1).

Malignancies associated with EBV and/or KS human herpesvirus are frequently found in patients infected with HIV. HIV may contribute to lymphomagenesis by acting directly on B lymphocytes as a critical microenvironmental factor in cooperation with EBV. The pathogenesis of EBV-associated lymphomas including LYG in people with HIV is considered the result of the concerted action of different factors, mainly including impaired immune surveillance, genetic alterations, viral infection, and chronic B-cell activation. LYG may be present in other immunosuppressive states than HIV, for example, patients with chronic lymphocytic leukemia [8–14].

Effective HAART is a cornerstone of KS treatment, because it significantly reduces inflammation, inhibits HIV replication, and improves immune responses against KSHV. Adequate control of HIV replication by HAART also has been associated with decreased plasma EBV DNA.

Treatment selection is based on histologic grade and underlying pathobiology with low-grade disease hypothesized to be immune-dependent and typically polyclonal and high-grade disease to be immune independent and typically oligoclonal or monoclonal. Methods of augmenting the immune response to EBV in low-grade LYG include treatment with interferon-α2b, whereas high-grade disease almost always requires immunotherapy [9, 15].

Corticosteroids are the most commonly used treatment for LYG, but although the neurologic and pulmonary symptoms often transiently improve, relapse is the rule, and they are not effective for long-term disease control [15, 16].
### Table 1  Differential diagnosis of lymphomatoid granulomatosis

| Differential diagnosis | Pattern and necrosis                                                                 | Cellular morphology                                                                 | Immunophenotype                                                                 |
|------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| **Malignant neoplasms**|                                                                                      |                                                                                    |                                                                                |
| Post-transplant lymphoproliferative disorder (DLPT) | A pattern of coagulative necrosis may be similar (DLPT polymorphic type)            | B-cell rich rather than T cells relatively depleted with slight atypia             | EBER+, CD30+/−, CD15−                                                       |
| Classic Hodgkin lymphoma | Often granulomatous pattern                                                        | Reed-Sternberg and Hodgkin (HRS) cells in a background of lymphocytes, histiocytes, plasma cells, eosinophils | HRS cells may be EBER+ or EBER−, CD30+, CD15+, CD20+/−, PAX5+, CD79a−          |
| Diffuse large B-cell lymphoma (DLBCL) associated with chronic inflammation | Diffuse pattern, Massive necrosis and angiocentric growth maybe present.              | EBV+ large B cells show centroblasts or immunoblastic Morphology with minimal inflammatory background | CD20+, CD79a, EBER+, CD30+/− (occasional) |
| Extramedullary plasmacytoma |                                                                                      |                                                                                    |                                                                                |
| Peripheral T-cell lymphoma, not otherwise specified | Lymphoma shows paracortical or diffuse infiltrates with effacement of the normal architecture | Cells may be small, medium-sized, large, anaplastic, or a mixture of small and large cells. | EBV+, but lacks B-cell markers Cells express CD3epsilon, CD2, CD56, and cytotoxic markers. |
| **Vasculitis**             |                                                                                      |                                                                                    |                                                                                |
| Inflammatory pseudotumor of the lung | Fibrosis is common, but necrosis absent.                                            | Mixed inflammatory infiltrates without atypia.                                     | Polyclonal plasma cells are abundant.                                       |
| Wegener’s granulomatosis | Fibrinoid vascular necrosis is uncommon.                                           | Inflammatory infiltrate contains abundant neutrophils, including neutrophilic microabscesses, | Capillaritis is a helpful diagnostic feature.                               |
| Allergic angiitis and granulomatosis (Churg-Strauss Syndrome) | Necrotizing vasculitis with eosinophilic pneumonia.                                 | Granulomatous inflammation with giant cells Lympocytes are relatively sparse.     | Changes of chronic asthma in bronchioles.                                  |
| **Interstitial pneumonia** | Underlying lung architecture intact without nodular lesions.                        | Interstitial infiltrate of lymphocytes, histiocytes, and fibroblasts vary according to the type of primary pathology. |                                                                                |
In a study conducted in the USA, at the National Cancer Institute, adult patients with high-grade LYG at diagnosis received combination chemoimmunotherapy with rituximab, prednisone, etoposide, vincristine, cyclophosphamide, and adriamycin, getting a complete response (CR) rate of 66%, but a progression-free survival (PFS) of only 40% with a median follow-up of 28 months. At the time of relapse, it was observed that patients would relapse with low-grade disease and can subsequently respond to IFN. With a median of 4 years, the overall survival of all patients with LYG treated with this strategy was 68% [16, 17].

Conclusions

LYG can lead to progressive pulmonary failure, central nervous system disease, or progression to overt EBV-positive lymphoma without appropriate recognition and management. Improvements in the modern understanding of the biology of LYG, particularly the precise role of EBV in its pathogenesis, offer promise in the development of improved management strategies.

Our case is interesting because it represents the clinical expression of three different viruses in one patient: HIV, HHV-8, and EBV-related LYG. Our institute has vast experience in the treatment of HIV-related and not related malignancies. We propose that treating concomitant infections, and improving underlying immunocompromise, in this case with antiretroviral therapy, allows the patient to improve and suppress the manifestations of this virus. A multidisciplinary approach and close follow-up are important in these cases to detect progression. Clinical improvement was documented by the disappearance or significant reduction of lung nodules.

Declarations

Ethics approval The study was performed with written consent.

Conflict of interest The authors declare no competing interests.

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