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LETTER TO THE EDITOR

Lymphomatoid granulomatosis mimicking cancer and sarcoidosis

Grosse Alexandra[1] · Grosse Claudia[1]

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Abstract

Two cases of misdiagnoses of lymphomatoid granulomatosis are discussed here. Lymphomatoid granulomatosis is an Epstein-Barr virus-associated lymphoproliferative disorder with aggressive behavior. Due to its rarity and many presentations, delay in diagnosis and treatment is common. Its histological features including large atypical B-cells, T cell predominance, angiocentricity, necrosis, and evidence of EBV-positive cells should elicit the diagnosis of lymphomatoid granulomatosis. The settings that are described here have not yet been described in the literature.

Keywords Lymphomatoid granulomatosis · Epstein-Barr virus · Pulmonary nodules · Misdiagnosis

Dear Editor,

A 77-year old asymptomatic male underwent routine check after bladder cancer treatment with cystectomy and ileum-conduit 5 years prior. Laboratory test results were unremarkable. Computed tomography (CT) of the chest and abdomen and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) revealed a solitary, metabolically active, 22 mm large nodule in the right lower lung lobe without lymph node or distant metastases. The patient underwent wedge resection of the pulmonary nodule (Fig. 1A–D). Intraoperative frozen sections demonstrated sheets of atypical cells and necrosis. Metastatic cancer was diagnosed on frozen sections. Bronchial carcinoma was in the differential. The cells were, however, negative for pancytokeratin and urothelial markers and positive for CD45 on postoperative immunostains. The majority of cells were CD20-positive large B cells, interspersed among small CD3-positive T cells. In situ hybridization (ISH) showed numerous Epstein-Barr virus (EBV)-encoded small nuclear RNA (EBER) positive cells surrounding large areas of necrosis. Immunoglobulin gene rearrangement (IGR) studies showed monoclonality. The patient was diagnosed with lymphomatoid granulomatosis (LYG) grade 3 (DLBCL IE) and was started on six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone. No other LYG manifestation evolved. Therefore, the patient received no further therapy and is now being closely followed-up.

A 64-year-old female presented with right-sided deafness, dizziness, and weakness in her extremities. CT of the chest showed multiple pulmonary nodules. Magnetic resonance tomography (MRT) of the cervical spine and brain showed lesions at the level of C2, in the right nasopharyngeal region (tuba eustachii) and the left brachium pontis (cerebelli). Complete blood count was unremarkable; lactate dehydrogenase, 491 U/l, and C-reactive protein, 26 mg/l, were elevated. Five years prior, she had been diagnosed with sarcoidosis based on multiple pulmonary nodules and enlarged metabolically active mediastinal lymph nodes on PET-CT. Lymph node biopsy at that time had demonstrated granulomatous inflammation and trans-bronchial lung biopsy had shown necrotizing acute and chronic inflammation. Now, her symptoms were related to neurosarcoidosis. The patient underwent biopsy of the nasopharyngeal lesion (Fig. 1E–H) and CT-guided biopsy of the cerebellar lesion. Biopsies revealed infiltration of lymphoid cells with scattered atypical cells and large areas of necrosis. Most cells were CD3-positive small T cells intermixed with CD20-positive large B cells. EBER-ISH showed scattered EBV-positive cells in the nasopharyngeal biopsy (grade 2) and numerous EBV-positive cells in the cerebellar biopsy (grade 3). The patient was diagnosed with LYG grade 3. IGR studies

✉ Grosse Alexandra
Alexandra.Grosse@usb.ch

[1] Institute of Pathology and Molecular Pathology, University Hospital Zurich, Rämistrasse 100, 8091 Zürich, Switzerland

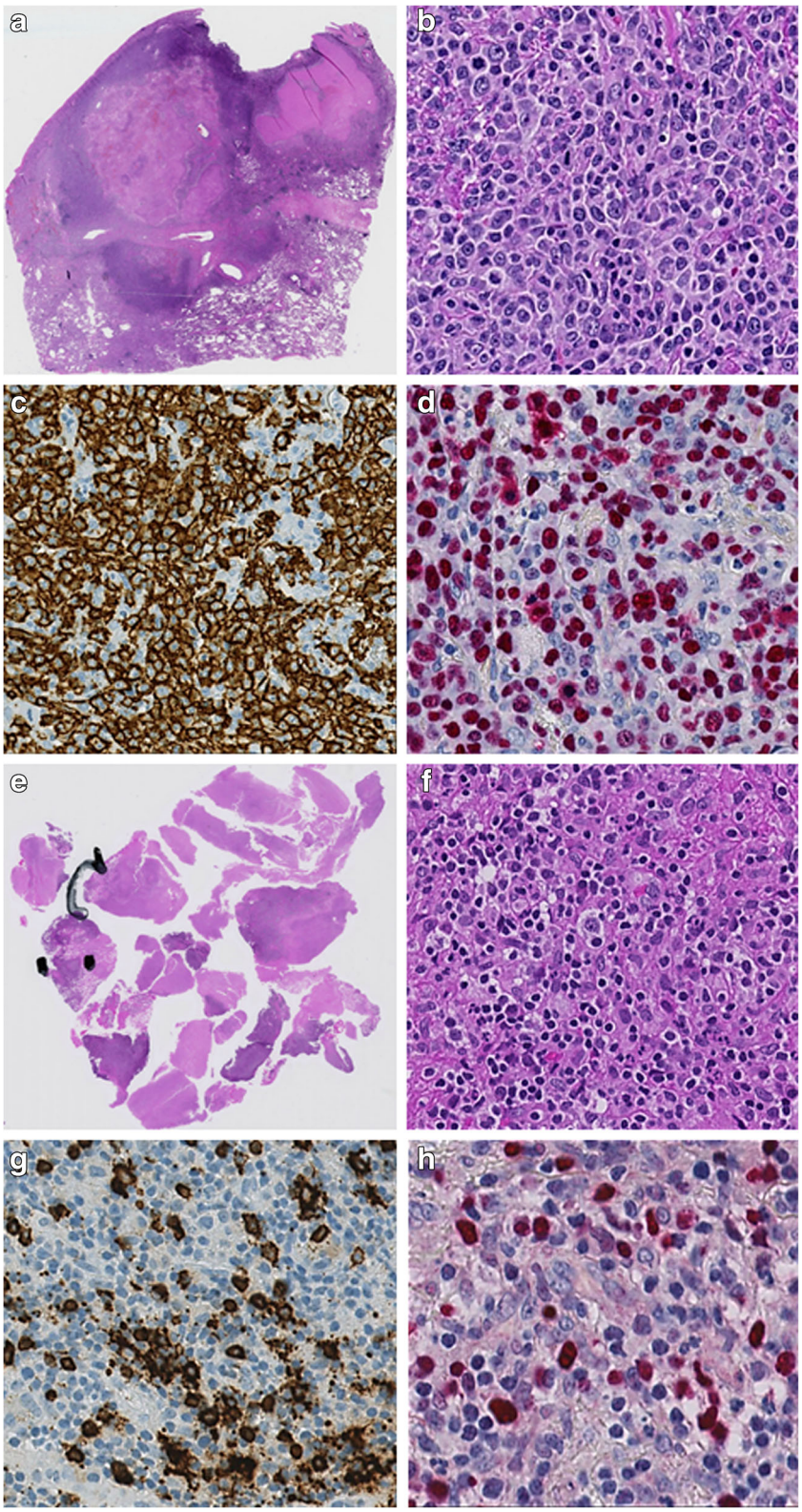

Fig. 1 **A** Hematoxylin and eosin staining of lung resection specimen shows a nodular lymphoid cell infiltrate, zones of necrosis, and angiocentric distribution. **B** At magnification, there are numerous large atypical cells, positive for CD20 immunostaining **C**, and Epstein-Barr virus (EBV)-positive by EBV in situ hybridization (grade 3) **D**. **E** Hematoxylin and eosin staining of the resection specimen from the right nasopharyngeal region. **F** At magnification, scattered large atypical cells are seen, positive for CD20 immunostaining **G**, intermixed with numerous small T-cells. **H** EBV in situ hybridization shows fewer EBV-positive cells (grade 2) compared with **D**

demonstrated oligoclonal rearrangement with transition to monoclonal rearrangement in the nasopharyngeal and monoclonal rearrangement in the cerebellar biopsy. FISH showed no break in the c-MYC gene (8q24). EBV-DNA PCR was 13,175 IE/ml in the whole blood and dropped to < 122 IE/ml under therapy. HIV screening was negative. Previous treatment with methylprednisolone was stopped, and based on the involvement of the central nervous

system (CNS), four cycles of rituximab, methotrexate (MTX), and cytarabin were initiated with slight regression of the lesions on MRT. Due to the radiological persistence of LYG manifestation, three cycles of immunochemotherapy with R-ICE (rituximab, ifosfamid, carboplatin, and etoposide) were started, followed by one cycle of rituximab, MTX, and cytarabin. Because of residual contrast enhancement on follow-up MRT, the patient finally underwent a sixth cycle of BCNU/Thiopeta as well as autologous stem cell transplantation (ASCT), resulting in complete remission to date. The initial trans-bronchial lung biopsy was re-evaluated, and EBV-positive cells were detected by EBER-ISH in the biopsy material.

Lymphomatoid granulomatosis (LYG) is a rare angiocentric B cell lymphoproliferation. First described in 1972 [1], it was historically considered a T cell lymphoma due to its T cell predominance [2, 3]. LYG can be diagnostically challenging due to many mimickers [4–7]. Biopsy is required for diagnosis including the histological features of polymorphic infiltrate, large atypical B-cells, necrosis, and lymphocytic vasculitis [8]. Prognosis is poor and median survival is around 14 months [9]. An overt state of immunodeficiency is not required, although patients have at least past EBV exposure by serology [8]. Lymphadenopathy is very rare, and caution should be taken to diagnose LYG in a setting of lymph node enlargement [8]. When multiple lesions are present or multiple organs are involved, multiple biopsies are recommended to avoid underestimation of grade [8]. There is no official therapeutic approach, however, LYG grade 3 generally requires a therapy similar to DLBCL. For long-standing CNS-LYG combined chemotherapy with cytarabin, which is standard therapy for CNS lymphoma, has proven to be effective [10].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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