Isolated Primary Lymphomatoid Granulomatosis of Central Nervous System

Bulent Cetin · Mustafa Benekli · Nalan Akyurek ·
Senem Senturk · Hayrettin Koklu · Esra Karakus ·
Ugur Coskun · Suleyman Buyukberber

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Abstract Lymphomatoid granulomatosis (LG) is an infrequent extranodal Epstein-Barr virus (EBV)-associated B-cell lymphoproliferative disorder characterized by angiocentric and angiodestructive polymorphic lymphoid infiltration. CNS is involved in one of every 4 patients, but isolated CNS involvement at presentation is rare. A 67-year-old man was admitted to our hospital because of visual impairment. Magnetic resonance imaging (MRI) revealed a suprasellar mass lesion isointense to gray matter on T1 and T2-weighted images. The hypothalamic/chiasmatic mass was resected through a transsphenoidal approach. Pathological examination of the biopsy specimen revealed large atypical, CD20-positive B-lymphocytes within a background containing numerous CD3-positive small T-lymphocytes and scattered admixed plasma cells and histiocytes. Necrotic areas and vascular infiltration by a mixed mononuclear cell infiltrate with scattered large atypical lymphoid cells was present. In situ hybridization for EBV showed few large cells both around blood vessels

and adjacent to the necrotic zone. This morphologic and immunophenotypic features was diagnostic for lymphomatoid granulomatosis. The patient was successfully treated with steroids, high-dose methotrexate and radiotherapy.

Keywords Lymphomatoid granulomatosis · Central nervous system · Methotrexate

Introduction

Lymphomatoid granulomatosis (LG) is an infrequent lymphoproliferative disorder characterized by angiocentric and angiodestructive Epstein-Barr virus (EBV)-positive B-cell proliferation associated with extensive reactive T-cell infiltration [1, 2]. Approximately two-thirds of cases are seen in males. Median age at presentation is in the fifth decade of life, although pediatric cases occur. The most common sites of involvement are lungs (90%) followed by skin (25–50%), kidneys (30–40%), liver (29%), and central nervous system (CNS) (26%) [3–5]. Spleen and lymph nodes are less often involved. Nearly all patients are symptomatic at presentation with fever, weight loss, joint pain, cough, dyspnea, and chest pain. Cutaneous involvement can be morphologically diverse with ulcerations, plaques, maculopapules and subcutaneous nodules. A variety of neurologic signs, including diplopia, ataxia, and mental status changes may be evident. Because LG can affect any site in the CNS, symptoms depend on which site is involved. On rare occasions, brain lesions may be the initial or the only clinical manifestation of the disease [6–13]. In patients without pulmonary symptoms, diagnosis may be significantly delayed. In patients with intracranial mass lesion, biopsy is useful for diagnosis. We herein present a patient with isolated CNS LG and discuss his management in light of the pertinent literature.

B. Cetin (✉) · M. Benekli · U. Coskun · S. Buyukberber
Division of Medical Oncology, Department of Internal
Medicine, Gazi University Faculty of Medicine, Besevler,
Ankara 06500, Turkey
e-mail: caretta06@hotmail.com

N. Akyurek · E. Karakus
Department of Pathology, Gazi University Faculty of Medicine,
Ankara, Turkey

S. Senturk
Department of Radiology, Goztepe Education and Research
Hospital, Istanbul, Turkey

H. Koklu
Department of Internal Medicine, Gazi University Faculty
of Medicine, Ankara, Turkey

Case Report

A 67-year-old man was presented with rapidly progressing bilateral visual impairment without headache. On admission, physical and neurologic examination revealed no abnormality except visual impairment. An ophthalmologic examination showed homonymous hemianopsia with suspected slowly enlarging mass involving the sellar region and optic chiasm. However, there was no evidence of overt papilledema or other abnormalities on either retina or optic vasculature. Visual acuity was 20/50 in both eyes, correcting to 20/30 in the right and 20/25 in the left. Cranial magnetic resonance imaging (MRI) after gadolinium enhancement revealed a 1.4 cm expansive solid mass in the suprasellar region infiltrating the optic chiasm. The lesion was isointense to gray matter on T1- and T2-weighted images, and showed intense enhancement (Fig. 1).

The hypothalamic/chiasmatic component of the mass was resected through transsphenoidal approach. Histopathology showed large atypical lymphocytes within a background infiltration of small lymphocytes, histiocytes, and occasional plasma cells. Necrotic areas and vascular infiltration by a mixed mononuclear cell infiltrate with scattered large atypical lymphoid cells were present (Fig. 2a). Large atypical lymphoid cells were stained with CD20, whereas more numerous small lymphocytes were positive with CD3. In situ hybridization for EBV-encoded small RNAs (EBER) showed a few large cells both around blood vessels and adjacent to the necrotic zone (Fig. 2b).

After a diagnosis of intermediate grade LG was made, the patient underwent complete staging work-up for

systemic lymphoma. Results of routine laboratory tests were normal. Positron emission tomography (PET-CT) with ^{18}F -fluorodeoxyglucose (18F-FDG) was negative. Cytologic analysis of cerebrospinal fluid (CSF) was negative for malignant cells. EBV PCR on CSF was not performed due to technical limitations. There was no overt evidence of compromised immunity and viral markers for hepatitis B virus surface antigen (HBsAg), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) were undetectable. He had already been put on steroids.

The patient was offered treatment along the lines of an aggressive primary CNS lymphoma. After eight cycles of high-dose methotrexate therapy followed by 50.4 Gy of radiation therapy, the patient recovered fully with complete radiologic remission. He remains in remission 12 months after the completion of his treatment.

Discussion

LG is an angiocentric and angi destructive EBV-positive B cell lymphoproliferative disease [1–4]. Extranodal involvement is pivotal. Pathogenesis of LG still remains unclear, but some investigators consider LG as a neoplastic B cell proliferation in response to EBV antigen stimulation [14, 15].

CNS involvement occurs in 30% of LG patients with nonspecific clinical features, including headache, blindness, cranial neuropathies, hemiparesis, altered consciousness, confusion, cerebrovascular syndromes, ataxia, seizures, parkinsonism, and dementia [3–5]. A number of inflammatory and demyelinating diseases may mimic LG such as multiple sclerosis, neurosarcoidosis, acute disseminated encephalomyelitis, and cerebral vasculitis syndromes. There are numerous reports of LG in immunocompromised hosts such as post-transplant setting and acquired immunodeficiency syndrome (AIDS) shortly after initiation of highly active antiretroviral therapy as a manifestation of immune reconstitution syndrome [16, 17]. On rare occasions, LG patients present with initial neurological symptoms without pulmonary abnormalities leading to delayed difficult diagnosis [6–13]. To date, less than 25 patients affected by primary CNS-LG have been reported in the literature (reviewed in 13).

World Health Organization (WHO) classification categorizes LG in the non-Hodgkin lymphomas (NHLs) as a neoplasm of mature B cells [1, 2]. Large lymphoid cells express CD20 and less frequently CD30, but not CD15. LG is graded according to the number of EBV-positive B cells and necrosis. Grade 1 lesions are composed of a polymorphous lymphoid infiltrate without cytologic atypia. Infrequent EBV-positive cells are identified by in situ hybridization with an EBV-encoded RNA probe.

Fig. 1 Sagittal contrast-enhanced T1-weighted MR image showing an enhancing hypothalamic/chiasmatic mass (arrows) in the suprasellar cistern. Hypophysis (star) and infundibulum (arrow head) are not affected

Fig. 2 **a** The infiltration is composed of large atypical lymphoid cells, small lymphocytes and histiocytes (HE, $\times 200$). **b** In situ hybridization for EBV-encoded small RNA (EBER) showing numerous cells both around blood vessels and adjacent to the necrotic zone (EBER, $\times 200$)

Infrequent large lymphoid cells are seen in a polymorphous background in grade 2 LG. EBV-positive cells are easily identified (5–20/high-power field [HPF]). Necrosis is common. Grade 3 lesions are characterized by extensive necrosis and numerous EBV-positive pleomorphic B cells (>50 /HPF). With these pathologic findings, grade 3 LG is considered a subtype of diffuse large B cell lymphoma (DLBCL) and treated as such. Our patient had grade 2 LG with readily recognized EBV-positive, CD20 positive lymphomatous large B cells.

Clinical prognosis in LG depends on pathologic grade and clinical presentation with a median survival of approximately 2 years [4, 5]. Because the disease is rare, optimal treatment is unclear. But LG is usually treated as per NHL guidelines according to the disease grade. Grade 3 LG is usually treated as DLBCL, and lower grades as indolent lymphomas. Steroid therapy is usually effective in patients with grade 1 disease, but high-grade LG requires aggressive multimodality treatment, including chemotherapy and radiotherapy. Rarity of isolated CNS LG makes treatment even more challenging. We opted to treat our patient as a primary CNS lymphoma with steroids, high-dose systemic methotrexate followed by radiotherapy. The patient responded well to treatment and remains in remission.

In conclusion, primary CNS LG is a rare disease that should be considered in the differential diagnosis of cerebral lesions. Treatment should include agents with good CNS penetration such as methotrexate or cytarabine in addition to steroids. Better understanding of the molecular pathogenesis of LG will provide clues to develop novel treatment strategies.

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