Epstein-Barr Virus Associated Cutaneous Angiocentric Immunoproliferative Lesion Showing Histologic Features of Classical Lymphomatoid Granulomatosis

Doo Hyun Chi, M.D., Joo Ryung Huh, M.D.*, Kyung Jeh Sung, M.D., Jai Kyoung Koh, M.D.

Department of Dermatology and *Pathology, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, Korea

We describe a patient with cutaneous angiocentric immunoproliferative lesion (AIL) associated with the Epstein-Barr virus (EBV). An organ system survey revealed no evidence of internal involvement. A skin biopsy specimen showed infiltrating cells involving mainly deeper dermis and subcutaneous tissue. An examination of the reticular dermis revealed polymorphous angiocentric and angioinvasive infiltrate containing some atypical lymphocytes and histiocytes. EBV encoded RNA (EBER) was demonstrated in lesional skin by the in situ hybridization technique. On the basis of these findings, we conclude that our case may represent a form of AIL associated with EBV showing histologic features of classical lymphomatoid granulomatosis. (Ann Dermatol 8:(2) 110–113, 1996).

Key Words: Angiocentric immunoproliferative lesion, Epstein-Barr virus

Lymphomatoid granulomatosis is a lymphoproliferative disorder characterized by multisystem polymorphous angiocentric and angioinvasive infiltrate containing atypical lymphocytes and histiocytes\textsuperscript{1,2}. It has a predilection for the lungs, but rarely is skin the only site of organ involvement\textsuperscript{1,3}. The term “angiocentric immunoproliferative lesion (AIL)” was introduced by Jaffe et al. to replace lymphomatoid granulomatosis and related disorders, including lymphocytic vasculitis and lethal midline granuloma\textsuperscript{4,5}. Recently it has been regarded as a subtype of cutaneous T-cell lymphoma (CTCL) and the Epstein-Barr virus (EBV) has been demonstrated as being associated with it\textsuperscript{6,7}. We describe a patient with EBV-associated AIL showing histologic features of classical lymphomatoid granulomatosis.

REPORT OF A CASE

A 61-year-old man had asymptomatic papules, plaques and nodules on his face, trunk and extremities for 6 months. An examination revealed violaceous, purpuric, indurated plaque on the right lower leg (Fig. 1). A physical examination indicated that he was normal except for the skin lesions. The family history, the past medical history and the review of systems were all unremarkable. The results of the following studies were within normal limits or negative: complete blood cell count, urinalysis, and liver function test. A roentgenogram of the chest was also normal. A biopsy specimen showed infiltrating cells involving mainly deeper dermis and subcutaneous tissue (Fig. 2). An examination of the reticular dermis revealed polymorphous angiocentric, angioinvasive lymphohistiocytic infiltrate (Fig. 3). Lymphocytes, atypical lymphoid cells, histiocytes and some eosinophils were visible around blood vessels, but necrosis was not observed. Examination

Received July 24, 1995
Accepted for publication December, 1995
Reprint request to: Doo Hyun Chi, M.D., Department of Dermatology Asan Medical Center College of Medicine, University of Ulsan Kangdong P.O. Box 145 Seoul, Korea
Phone: (02)224-3460; fax (02)486-7831

110
of the subcutaneous tissue revealed relatively monomorphous lymphoid cell infiltrate (Fig.4). The immunohistochemical studies demonstrated positive labeling of the infiltrating lymphoid cells for CD45RO(UCHL-1) and CD4, whereas CD20(L-26), CD8 and CD30(Ki-1) showed no immunoreactivity. A gallium scan, bone marrow biopsy and brain-chest-abdomen-pelvis CT revealed no evidence of internal organ involvement. Serum protein electrophoresis showed no abnormal bands and the T4/T8 ratio was 0.25 in the peripheral blood. Serum IgE level was elevated at 1714 IU/l (normal < 100). These clinical and histopathologic findings were consistent with a diagnosis of cutaneous AIL and EBV studies were done in serum and lesional tissue. Antibodies to viral capsid antigen (VCA), early antigen (EA) and the Epstein-Barr nuclear antigen (EBNA) were all positive except for IgM-anti-VCA in serologic studies and the titers were regarded as significantly elevated based on the background data of the general population. In addition, EBV encoded RNA (EBER) was demonstrated in lesional tissue by the in situ hybridization technique. EBER positive cells were observed around dermal blood vessels and subcutaneous tissue corresponding to lymphoid cells in lesional H & E tissue sections (Fig. 5). EBER transcripts were also demonstrated in the nucleus of atypical lymphoid cells infiltrating the vessel wall. The histiocytic cells showed no positive signals. Treatment was started with oral cyclophosphamide, 100 mg daily and prednisolone, 60 mg daily. At the follow up 4 weeks later, there was a great deal of improvement of the skin lesions. He has been in remission with the same dose of cyclophosphamide and variable dose of prednisolone for 15 months.

**DISCUSSION**

In 1972, Liebow et al. described 40 cases of a new clinicopathologic entity entitled lymphomatoid granulomatosis. They described the process as an angiocentric and angiodestructive lymphoreticular proliferative and granulomatous disease. It has a predilection for the lungs, but also involves skin in roughly 40% of cases. The cutaneous lesions usually appear simultaneous with pulmonary lesions but are the sole manifestation in up to 20% of cases and may precede systemic disease by 8-9 years. The term "angiocentric immunoproliferative lesion (AIL)" was introduced by Jaffe et al. to replace lymphomatoid granulomatosis and related disorders, including lymphocytic vasculitis and lethal midline granuloma. They graded cases into three histologic categories: grade I, II, and grade III lesions represent overt malignant lymphoma, also termed "angiocentric lymphoma." The clinical course of AIL is chronic if localized, but dissemination to other organs is usually accompanied by aggressive disease and often rapidly terminates in a hemophagocytic syndrome simulating malignant histiocytosis. In our case, some of the lymphoid cells in dermis showed significant atypia, but they lacked marked nuclear aberrations and necrosis was absent. To be diagnosed as grade II AIL, virtually all lymphoid cells show atypicality and necrosis are abundant. Therefore, this case is on the borderline between grades I and II AIL, although relatively monomorphous lymphoid cell infiltrate mimicking subcutaneous T-cell lymphoma was observed in subcutaneous tissue. Subcutaneous T-cell lymphomas appear to be distinguishable from our case by virtue of the absence of an angiocentric growth pattern, a predilection for the subcutaneous tissue of the lower extremities and trunk, for the production of systemic signs and symptoms and for an aggressive clinical course that may be complicated by a fatal hemophagocytic syndrome. In the case reported by Burg et al., the cells expressed an immature, but activated, T-cell phenotype CD1+, CD3+, CD4+, CD8-, CD30+, dissimilar to the CD45RO+, CD4+, CD8-, CD30- T-cells in our case. However, it is interesting to note that the absence of extensive necrosis in both cases and some cases of T-cell lymphomas that have been associated with hemophagocytosis have been classified as angiocentric lymphomas; thus there is a possible link between these two disorders. The association of EBV with AIL or angiocentric lymphoma is relatively consistent. Recently Su et al. proposed five distinct clinicopathologic subgroups of CTCL and recognized three distinct subtypes of EBV-associated CTCL, among them the most remarkable was the angiocentric T-cell lymphoma or lymphomatoid granulomatosis (type II CTCL). However, some authors hypothesized that most cases of lymphomatoid granulomatosis involving the lung represent a proliferation of EBV
Fig. 1. Violaceous, purpuric, indurated plaque on the extensor surface of the right lower leg.

Fig. 2. Low-power view demonstrates infiltrating cells mainly in deeper dermis and subcutaneous tissue (H&E × 10).

Fig. 3. Higher magnification showing polymorphous, angiocentric, angioinvasive lymphohistiocytic infiltrate (H & E × 200).

Fig. 4. High power view of the subcutaneous tissue showing relatively monomorphous lymphoid cell infiltrate (H & E × 200).

Fig. 5. EBER positive cells are seen around a blood vessel in subcutaneous tissue (× 100).

Infected B-cells with a prominent T-cell reaction and vasculitis, distinguishing these cases from angiocentric T-cell lymphomas. The common features of EBV-associated CTCLs are resistance to conventional chemotherapy, poor prognosis and the terminal manifestation of a hemophagocytic syndrome. However, in our case, the response to conventional chemotherapy was considerable and hemophagocytosis was not identified. A clonotypic proliferation of EBV genomes has been demonstrated in EBV-associated T-cell lymphoma,
which suggests a monoclonal proliferation of neoplastic T cells and also EBV genomes. The presence of repeated elements in the genome facilitates the detection of viral nucleic acids by a variety of hybridization techniques as well as the characterization of the clonality of virus infected cells. The abundant expression of EBER transcripts makes possible the sensitive detection of latent infection in EBV-associated tumors. Latent gene products are important because of their growth-regulating and -transforming properties; the expression of viral genes leads to the expression of a variety of cellular proteins including the adhesion molecules and BCL-2, an inhibitor of apoptosis or programmed cell death. Therefore, lymphoid cells in EBV-associated AIL may show specific tropism for the endothelium of blood vessels (angiocentricity) in skin and the immortalization of infected cells occurs. Further studies will help characterize in more detail the exact mechanism of EBV in the pathogenesis of AIL.

REFERENCES