A rare variant of generalized granuloma annulare presenting with chronic Epstein-Barr virus infection: coincidence or association?

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KEY WORDS

generalized granuloma annulare, Epstein-Barr virus

SUMMARY

We report a rare variant of generalized granuloma annulare (GGA) in a 62-year-old male patient. The patient presented with large, annular, violaceous patches on the upper arms and thighs. Histological findings were consistent with interstitial granuloma annulare. In addition, high titers of Epstein-Barr Viral Capsid Antigen (EBV VCA) and EBV Nuclear Antigen (EBVNA) antibodies were found. In-situ hybridization did not reveal EBV RNA in the skin lesions. Immune dysregulation in the setting of chronic EBV infection has been suggested as a contributing factor to the development of this rare variant of GGA.

Introduction

Granuloma annulare (GA) is an asymptomatic skin lesion that most often presents as dermal papules and plaques arranged in an annular configuration. Several clinical variants exist, including localized, generalized, subcutaneous, and perforating forms. Although the various types of GA share common histological findings, the clinical presentation can be quite different. For example, compared to the localized form of granuloma annulare, the generalized form typically affects an older population, has a more protracted course, can involve any area of the skin, and shows poorer response to therapy (1). An erythematous patch variant of GA also exists, characteristically lacking the papular component that is often seen in classic GA (2). This particular variant is very rare, with only seven cases reported in the literature (1, 2).

Generalized granuloma annulare (GGA) has rarely been reported to occur with viral infectious processes. A literature search revealed associations with HIV (3), resolved varicella-zoster lesions (4), and hepatitis B (5) and hepatitis C (6) infections. To our knowledge, there have only been two cases of GA associated with EBV reported in the literature (7, 8). We report a case of the rare erythematous patch variant of GGA in a patient with elevated EBV titers and consider the possible relationship between GA and EBV infection.

Case Report

A 62-year-old Caucasian male presented with a 4-year history of an asymptomatic skin rash involving all four extremities. The lesions began as brownish-yellow macules on his upper thighs and arms, but then slowly spread centrifugally to form wide circinate, bluish-red patches. The patient was unable to identify any precipitating factors. His past medical history was significant for hypertension, chronic heart failure, and diet-controlled diabetes mellitus. He had been on the following medications for the previous 10 years: captopril, digoxin, guaiafenesin, aspirin, and potassium powder. His family history was non-contributory.

On physical examination, several annular, bluish-red patches up to 15 cm in diameter were present on the upper thighs, arms, and shoulders (Figure 1a). A brownish-yellow hue was seen at the edges of several lesions (Figure 1b). No lymph node enlargement was noted.

The work-up included a CBC with differential, liver function tests, glycosylated hemoglobin, triglycerides, electrolytes, BUN, and creatinine, all of which were within normal limits. Cholesterol and blood glucose were borderline elevated, measuring at 200 mg/ml and 137 mg/dl, respectively. Serum immunoelectrophoresis, complement levels, thyroid profile, rheumatoid factor, peripheral blood circulating lymphocytes, and phenotype were all normal as well. Tests for hepatitis B, hepatitis C, syphilis, HIV, and Lyme disease were negative. Epstein-Barr viral capsid antigen (VCA) IgG antibodies were elevated on several occasions (1:640 to 1:1,280, reference range < 1:160), as were EBV nuclear antigen (EBNA) antibodies, with titers ranging from 1:1,280 to 1:320 (normal < 1:160). EBV VCA IgM antibodies were negative.

A biopsy from the advancing edge of a patch on the right thigh showed an interstitial infiltrate composed of lymphocytes, histiocytes, and occasional multinuclear cells with areas of degenerated collagen (Figure 2a). A

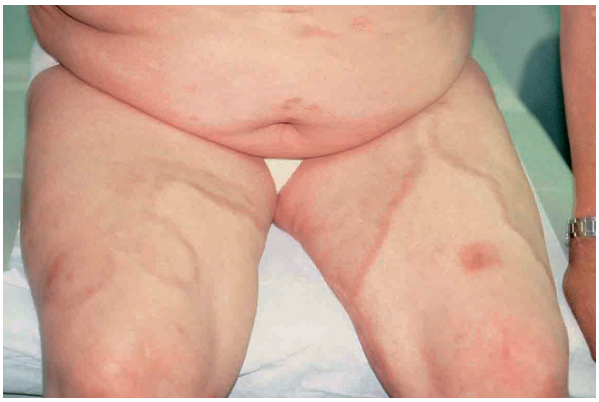

Figure 1a. Large, annular, bluish-red patches on the upperthighs resembling erythema annulare centrifugum.

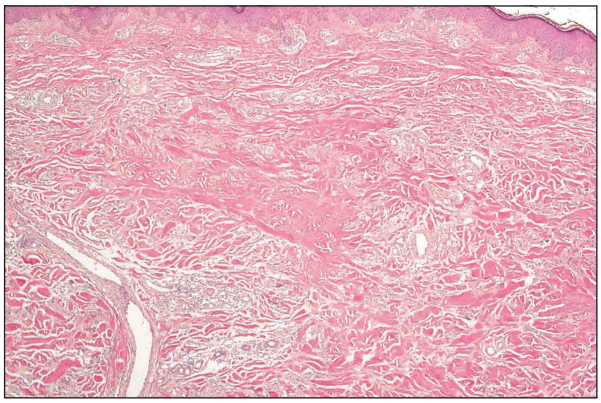

Figure 2a. Interstitial infiltrate of lymphocytes and histiocytes with areas of degenerated collagen (hematoxylin-eosin, original magnification ×10).

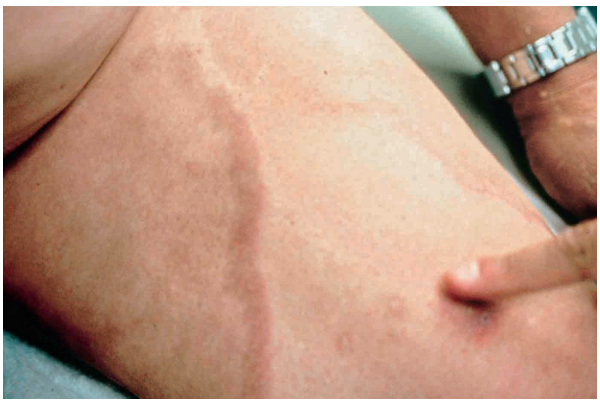

Figure 1b. Brownish-yellow hue at the edge of the patch on the left thigh.

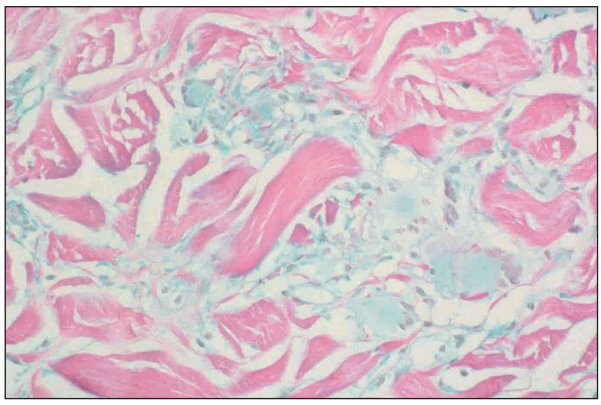

Figure 2b. Fair amount of mucin present in the areas of degenerated collagen (colloidal iron, original magnification ×20).

colloidal iron stain demonstrated a moderate amount of mucin (Figure 2b). The epidermis was unremarkable. The in-situ hybridization technique did not detect any EBV RNA in the sample.

Because the lesions were asymptomatic, our patient decided not to undergo any treatment.

Discussion

The first case of GA associated with EBV infection was reported by Spencer et al. in 1988. They described a patient with an annular lesion that resembled GA but lacked the characteristic histological finding of necrobiosis, mucin deposition, and a lymphohistiocytic infiltrate (8). Instead, this patient had a predominantly neutrophilic infiltrate, raising the question as to whether this was indeed GA. More recently, Park et al. reported a case of GGA in the setting of an acute EBV infection (7). They described a 2-year-old boy that developed a symmetric, flesh-colored to erythematous nodular eruption on the trunk and extremities 1 month after having mononucleosis-like symptoms. Laboratory data revealed 1% atypical lymphocytes, elevated hepatic aminotransferases, and a positive EBV VCA IgM, suggesting an acute EBV infection.

The etiology of GGA still remains largely unknown. One theory proposes vasculitis as the inciting event in GA. A study by Dahl et al. gave rise to this idea because he was able to demonstrate vasculitic changes in the tissue specimens of patients with GA (15). More recent case series, however, failed to confirm this (16, 17). The fact that certain diseases tend to cluster with GGA may provide some insight into its pathogenesis. The prevalence of inflammatory thyroid disease and connective tissue disease in these patients suggests that an underlying autoimmune phenomenon may play a role in the pathogenesis of GA.

There is also evidence that GGA may be a type IV delayed hypersensitivity reaction to local or systemic stimuli (18, 19). A study by Fayyazi et al. provided convincing evidence of this, as they were able to show in tissue samples of patients with GA that a large number of CD3+ lymphocytes expressed interferon (IFN)-δ (20). Further studies revealed that IFN-δ^+ Th-1 lymphocytes could cause a delayed-type hypersensitivity reaction by inducing macrophage maturation and release of TNF-α and matrix metalloproteinases (MMPs) (20). This pro-inflammatory milieu could account for the classic histopathological picture—a necrobiotic core surrounded by a lymphohistocytic infiltrate—that is seen in GA.

Several precipitating factors have been identified in patients with GGA, including sunburn, physical trauma, insect bites, and flu-like illnesses (1). The latter event is of particular interest because viral infections such as HSV, HIV, hepatitis, and EBV have been associated with GGA. Although our patient was unable to recall a history of a viral prodrome, he had a high titer of EBV VCA IgG antibodies and EBNA antibodies. VCA IgM antibodies were negative, however, suggesting that this patient was most likely a chronic carrier.

Infection with EBV results in both humoral and cellular immunity. Although the finding of antibodies directed against viral structural proteins and antigens is important for the diagnosis of infection, the cellular immune response is more important for the control of EBV infection (21, 22). Th-1 cells preferentially mediate a cellular immune response by secreting cytokines such as IFN-γ. Th-2 cells secrete IL-10, which stimulates B cell maturation and antibody production, but it also inhibits IFN-γ synthesis and antigen presenting cells. Interestingly EBV, like other gamma herpes viruses, is able to encode several cellular homologs that can modulate the host's immune system (23). For example, the EBV gene encodes a protein called BRCF1 that has an approximately 70% amino acid identity to IL-10 polypeptide (23). Studies in both mouse and human models have shown that BRCF1 has functional IL-10 cytokine activity (23). EBV also encodes for a BARF1 protein, which functions as a soluble receptor for human colony stimulating factor 1 (CSF-1) and prevents CSF-1 from binding to its native receptor (24). CSF-1 is known to induce proliferation of bone marrow macrophage progenitor cells and stimulate release of TNF-α and IFN-α from mononuclear cells (25). Therefore the ability of EBV BARF1 to inhibit the effect of CSF-1 results in impaired cytokine release from mononuclear cells and ultimately an impaired cellular immune response to EBV.

In summary, chronic EBV infection may suppress cell-mediated immunity by expressing cellular homologs that inhibit Th-1 cells and macrophages. As mentioned above, Th-1 cells and macrophages appear to be the targets of EBV encoded proteins BRCF1 and BARF1, respectively. We speculate that, in this particular case, the relative depression of Th-1 cells and macrophages caused by chronic EBV infection led to the atypical presentation of this patient's lesions. There is always the possibility that this patient's clinical presentation and elevated EBV titers were entirely coincidental. It should also be mentioned that high titers of EBNA or EBV VCA antibodies have occasionally been found in healthy carriers of EBV (22, 26). Still, the idea that chronic EBV infection can result in immune dysregulation and in some way alter the morphology and presentation of GA is provocative and warrants further consideration.

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