A 2-year-old boy was referred for multiple skin-colored to erythematous nodules, symmetrically scattered on the trunk and both extremities for 3 weeks (figure 1A, B). Two months previously, he had visited the pediatrician for fever, cough, sputum, and rhinorrhea. He had not received any vaccination previously, he had visited the pediatrician for fever, cough, sputum, and rhinorrhea. He had not received any vaccination during pregnancy. 

The laboratory data revealed leukocytosis (white blood cell count: 19,500/µL; aspartate transaminase: 103 U/L; reference range, 3.9-9.7 U/L) and elevated aminotransferases (aspartate transaminase: 103 U/L; reference range, 5-40 U/L, and alanine transaminase: 193 U/L; reference range, 8-41 U/L). Epstein-Barr virus (EBV) viral capsid antigen (VCA) IgM and EBV-early antigen (EBV-EA) IgG were positive while EBV nuclear antigen (EBNA) and other markers of viral hepatitis were negative, which suggested EBV-induced acute hepatitis, one of the clinical manifestations of acute EBV infection. From his clinical symptoms, hepatitis and EBV-associated viral markers, the diagnosis of infectious mononucleosis was made and he was managed conservatively. During follow-up, he complained of enlargement of both cervical lymph nodes and skin lesions. The lymph node biopsy revealed cervical lymphadenitis with positive results in EBV in situ hybridization. The skin biopsy showed interstitial infiltration of histiocytes and giant cells intermixed with degenerative collagen bundles, and mucin deposition in alcian blue staining (figure 1C, D). The clinicopathological features supported generalized granuloma annulare (GGA). He was treated with acyclovir (195 mg daily) for 8 days, but the skin lesions did not improve until the administration of oral (prednisolone, 5 mg daily) and topical corticosteroids (methylprednisolone aceponate 0.1%, twice daily) for 2 weeks.

GGA, a rare variant of granuloma annulare (GA), has been defined as lesions that occur symmetrically on the trunk and both extremities [1]. Clinical associations between GA and systemic disorders have been reported, such as diabetes mellitus, malignancies, thyroid diseases, and viral infections [2]. GGA is more associated with systemic diseases than localized GA, but it has only exceptionally been reported together with infectious processes. There have been some reports that GGA occurred in patients infected with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus [2]. Infection with EBV is a well-recognized cause of infectious mononucleosis, which is characterized by fatigue, fever, lymphadenopathy, and mild hepatitis. Our patient had no other systemic disorders suspected as a possible event associated with GGA development, except the acute EBV infection. To date, there has been only one case report of a GA-like eruption with chronic EBV infection [3]. In that report, however, the histological findings did not show typical features of GA because neutrophils were present, and both degenerative collagen and mucin deposition were absent [4]. Even though we cannot be certain of a connection between GGA development and acute EBV infection, one of the possible influential hypotheses of their relationship is the T-cell mediated hypersensitivity reaction [4]. The cytokines released from activated macrophages and fibroblasts in GA have been demonstrated in biopsy samples in previous reports, and these cytokines may result in the degeneration of elastic tissue and collagen, leading to the granulomatous reaction [5]. EBV antigens upregulate cytokines and human cytokine receptors, which may be important in modulating the host immune system and allowing the persistent infection [6]. Hence the ability of EBV to modulate cytokines might be the initiating point of the T-cell mediated systemic hypersensitivity reaction, causing GGA.

To our best knowledge, this is the first case of GGA possibly associated with acute EBV infection, with typical GA histological findings.


Dramatic response of recalcitrant warts as a side effect of colorectal cancer treatment with oral capecitabine

Antimitotic drugs bleomycin or 5-fluorouracil (5FU) have been used intraradionally or topically for plantar warts refractory to conventional treatment but their toxicity precludes systemic use for a benign condition. Capecitabine is an oral 5-FU prodrug used in breast and colorectal cancer. We report the first case of wart regression on capecitabine. A 49-year-old man had prolonged bilateral plantar warts which massively involved his toes (figure 1A) and had gradually spread to his right knee and left fingers. Pain, inability to walk, and difficulty in wearing shoes resulted in chronic unemployment and severely impaired his quality of life. The clinical diagnosis of warts was confirmed on skin biopsy but in situ hybridization was negative for HPV subtypes 6, 11, 16, 18, 31, 33 and 51. There was no evidence of immunodeficiency. Blood tests for HIV and hepatitis were negative. Complete blood counts with T-cell and B-cell subsets, and serum electrophoresis were normal. Over a ten-year period, he underwent multiple topical treatments: repeated surgery, salicylic acid, cidofovir, along with systemic drugs: oral acitretin, subcutaneous alpha interferon, without improvement. Carbon dioxide laser and intralesional bleomycin had to be discontinued because of intolerable pain. He was diagnosed with a rectal adenocarcinoma and received a neoadjuvant chemoradiotherapy with oral 1,650 mg capecitabine (800 mg/m²) b.i.d. for five weeks. Within about four weeks after initiation, all the warts progressively and almost completely resolved, except for residual mild hyperkeratosis on the big toes (figure 1B). Adverse effects were mild neutropenia (1.55 G/L) and diarrhoea without weight loss. When colorectal surgery was performed, only a residual focus of rectal adenocarcinoma was found. Thereafter, he received adjuvant chemotherapy with oxaliplatin and 5FU for ten cycles. No recurrence of warts has been observed for one year.

Near complete regression of recalcitrant warts on oral capecitabine (n4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine; Xeloda®) as a beneficial side effect of cancer treatment has not been previously documented. Wart regression during cancer treatment with cytostatic drugs is likely to be underreported, because they are overlooked or considered a minor problem in comparison with visceral cancer. Capecitabine is a prodrug for 5FU, an effective intralesional or topical drug for the treatment of warts. 5FU may inhibit the development of viral warts by interfering with nucleic acid synthesis of either the virus particles or the proliferating epithelial cells. HPV-infected cells grow more rapidly and probably incorporate fluorouracil at an increased rate as compared with healthy tissue [1]. In our patient, further adjuvant treatment with 5FU may have prevented delayed recurrence. Although the toxicity of antimitotic drugs usually precludes their use as a systemic therapy for a benign condition such as warts, their risk-benefit ratio might be reconsidered in cases of disabling warts with severe quality of life impairment. Cases of plantar warts successfully treated by isolated limb infusion with melphalan and actinomycin D have been reported [2, 3]. These treatments caused notable pain but no additional major toxicity was reported. Oral treatment with capecitabine appears more feasible. Its most common side effects – hand-foot syndrome, diarrhoea, anaemia, asthenia, stomatitis and neutropenia [4] – may require temporary withdrawal or dose reduction, but are usually reversible. Besides, cutaneous side effects of capecitabine have already been described, such as inflammation of actinic keratoses [5], which also suggests elimination of proliferating epithelial cells, as in wart regression, or vitiligo repigmentation [6], which can be considered beneficial.

We suggest that, in a subset of chronic disabling plantar warts, the safety and efficacy of systemic treatment with oral capecitabine should be evaluated.