Sweet’s Syndrome Complicated by Kikuchi’s Disease and Hemophagocytic Syndrome which Presented with Retinoic Acid-inducible Gene-I in both the Skin Epidermal Basal Layer and the Cervical Lymph Nodes

Tomohiro Koga¹, Kanako Takano¹, Yoshiro Horai¹, Satoshi Yamasaki¹, Hideki Nakamura¹, Akinari Mizokami², Koichi Ohshima³ and Atsushi Kawakami¹

Abstract

A 21-year-old man was admitted to our hospital with a fever, erythema, cervical lymphadenopathy and pancytopenia. A diagnosis of Sweet’s syndrome (SS) with Kikuchi’s disease (KD) and hemophagocytic syndrome (HPS) was made based on the results of a bone marrow aspiration along with the results from biopsy specimens of the brachial skin and a cervical lymph node. The expression of retinoic acid-inducible gene-I (RIG-I) in the skin epidermal basal layer as well as in a cervical lymph node was revealed through immunohistochemistry. He successfully entered remission through treatment with prednisolone. This findings of this case indicate that when SS with KD presents as HPS, it may suggest an association with an RIG-I-related innate immunity.

Key words: hemophagocytic syndrome, Kikuchi’s disease, retinoic acid-inducible gene-I, Sweet’s syndrome


Introduction

Sweet’s syndrome (SS) is characterized by a multitude of clinical symptoms, physical features and pathological findings including fever, neutrophilia, tender erythematous skin lesions (papules, nodules and plaques) and the presence of a diffuse infiltrate that consists predominantly of mature neutrophils that is typically located in the upper dermis (1, 2). The pathogenesis of Sweet’s syndrome is unknown. However, it has been suggested that Sweet’s syndrome is simply a hypersensitivity reaction, as the syndrome is commonly associated with infections, autoimmune diseases, inflammatory bowel disease, malignancy and drugs.

Histiocytic necrotizing lymphadenitis, or Kikuchi’s disease (KD), was originally described in young women and is a rare, benign condition with no known cause that is typically characterized by cervical lymphadenopathy and the presence of a fever (3, 4). Although the pathogenesis of KD is not yet known, the clinical presentation, course and histologic changes associated with the disease suggest that it is related to the immune responses of the T cells and the histiocytes to an infectious agent.

Both SS and KD response well to treatment with prednisolone, and are generally identified in patients with viral infections. However, the presence of both diseases in a patient is rare, and the pathogenetic mechanisms responsible for these diseases are not yet well understood. We herein report the findings of a case of SS complicated by both KD and hemophagocytic syndrome (HPS) which presented with retinoic acid-inducible gene-I (RIG-I) in both the skin epidermal basal layer and in the cervical lymph nodes.

Case Report

A 21-year-old man who had previously been in good

¹Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University, Japan, ²Department of Rheumatology, Nagasaki Municipal Hospital, Japan and ³Department of Pathology, Kurume University School of Medicine, Japan

Received for publication December 17, 2012; Accepted for publication April 8, 2013

Correspondence to Dr. Tomohiro Koga, tkogal1@me.com
health complained of an intermittent fever, the swelling of a cervical lymph node and skin rashes on his face and both upper arms. He was treated with azithromycin for 3 days, but the treatment was not effective. The laboratory testing revealed pancytopenia. He was admitted to our hospital for further evaluation. He had no family history of either collagen diseases or hematologic disorders. Upon admission, a physical examination revealed the presence of several round erythematous plaques on his face (Fig. 1a) and shoulders (Fig. 1b). He had multiple right anterior cervical lymph nodes that measured between 2 and 3 cm. He did not exhibit hepatosplenomegaly, and there were no unusual findings noted during an inspection of his oral cavity. A laboratory investigation was performed with the following results: a hemoglobin level of 11.8 g/dL; a white blood cell count (WBC) of 2.0×10^3/μL (neutrophils 89%, lymphocytes 10% and monocytes 1%); a platelet count (PLT) of 58×10^3/μL and a erythrocyte sedimentation rate of 46 mm/h. Most of his serum chemistry test results were normal, including aspartate aminotransferase, alanine aminotransferase, bilirubin, electrolytes, lipids, albumin, creatinine, blood urea nitrogen, and ferritin. However, abnormal levels were reported for C-
ANCAs). The serum IgG level and the concentration of the dase anti-neutrophil cytoplasmic autoantibodies (MPO-cytoplasmic autoantibodies (PR3-ANCAs) and myeloperoxidase (MPO-ANCAs)) were all negative: antinuclear antibody (ANA), anti-double-stranded (ds) DNA antibody, anti-Jo-1 antibody, anti-SS-A antibody, anti-SS-B antibody, proteinase-3 anti-neutrophil cytoplasmic autoantibodies (PR3-ANCAs) and myeloperoxidase (MPO-ANCAs). The serum IgG level and the concentration of the complement components were normal. A urinalysis revealed no abnormalities. The (1, 3) β-d-glucan assay did not detect any fungal species. There was no serologic evidence of any of the following: active Varicella zoster virus (VZV), Epstein-Barr virus (EBV), Cytomegalovirus (CMV), human herpesvirus 6 (HHV-6) or any of the 7 infections that can be identified using the Herpes multiplex PCR. A serum test for human imunodeficieny virus (HIV) antibody that was administered 4 weeks after the onset of the disease was negative. A cervical CT scan detected swelling in the supraclavicular lymph nodes as well as in the deep cervical lymph nodes. A thoracic and abdominal CT scan that utilized gallium scintigraphy showed no additional areas of lymphadenopathy or any evidence of malignancy. A brachial skin biopsy indicated SS (Fig. 2a, b). Retinoic acid-inducible gene-

Figure 3. A lymph node microscopic examination revealed an effaced nodal architecture with extensive apoptosis and confluent necrosis (a: Hematoxylin and Eosin (H&E) staining, original magnification ×40, the bar scale represents 250 μm). The viable cells mainly consisted of small lymphocytes and histiocytes. Phagocytosed cellular debris and peripheral crescentic nuclei were found. (b: H&E staining, original magnification ×200, the bar scale represents 50 μm). Immunohistochemical stains showed CD68-positive plasmacytoid monocytes and histiocytes. (c: DAB and H&E staining, original magnification ×40, the bar scale represents 250 μm; d: DAB and H&E staining, original magnification ×200, the bar scale represents 50 μm). Immunofluorescence staining was performed using a rabbit anti-RIG-I antibody with a tetramethyl rhodamine isothiocyanate (TRITC)-conjugated secondary antibody (red). The status of the nucleus was observed using Hoechst staining (blue). (c: negative control, d: the patient, original magnification × 40, the bar scale represents 100 μm.)
The patient was diagnosed with SS complicated by HPS based on the above findings. Adult onset Still’s disease complicated by HPS was not a plausible diagnosis due to the absence of arthritis and hyperferritinemia at the initial manifestation. However, we could not rule out paraneoplastic SS, so we performed a cervical lymph node biopsy that revealed a focal proliferation of reticular cells accompanied by extensive nuclear debris as well as several histiocytes (Fig. 3a, b). Immunohistochemical stains revealed CD68-positive plasmacytoid monocytes and histiocytes (Fig. 3c, d). The expression of RIG-I in the cervical lymph nodes was also confirmed (Fig. 3e, f). These findings were consistent with a diagnosis of KD. Taken together, we made the diagnosis of SS with KD and HPS, so prednisolone treatment (30 mg) was initiated as a result. Following the treatment, the patient recovered from the disease symptoms including the fever, skin lesions and lymphadenitis, and his levels of WBC, PLT, LDH and CRP returned to normal (Fig. 4). The patient was discharged on hospital day 20. Following discharge, the dose of prednisolone was tapered off over 2 months without a recurrence of the disease.

Discussion

There have been few reports of cases of SS complicated by KD. Ito et al. described the first case of SS with KD, which was confirmed through a skin biopsy and an inguinal lymph node biopsy (6). The patient responded well to oral prednisolone therapy, and the case was thought to be associated with viral infections in light of the clinical course. There has also been a report of an adult-onset HHV-7 infection that presented as necrotizing lymphadenitis and SS (7). Although a hypersensitivity reaction to an eliciting bacterial, viral or tumor antigen may promote the development of SS, the pathogenesis of SS remains to be definitively determined. The effects of cytokines have an etiologic role in the development of SS symptoms and lesions (8, 9). In the present case, we confirmed the expression of RIG-I in the skin epidermal basal layer and in the cervical lymph nodes. RIG-I is a cytoplasmic protein regarded as a cytoplasmic receptor for dsRNA and serves to recognize viruses such as measles, mumps, parainfluenza virus and respiratory syncytial virus (RSV) (10). In addition, immunohistochemical studies have revealed high levels of RIG-I expression in epidermal cells with psoriasis (5), in the macrophages associated with atherosclerotic lesions (11) and in the glomeruli of lupus nephritis (12). In this case, there is no evidence of psoriasis-like skin lesions, autoimmun disease or atherosclerosis. The clinical presentation and the therapeutic response suggest that a viral infection was the cause of the RIG-I expression, even though our patient had no serological evidence of viral infection (including EBV, herpes simplex virus, CMV and HHV-7). In general, HPS is a potentially fatal disorder due to the cytokine dysfunction that results in an uncontrolled accumulation of activated T lymphocytes and activated histiocytes (macrophages) in many organs. Treatment should be initiated immediately when the patient fulfills the clinical criteria for HPS, since the delay of therapy may lead to irreversible multi-organ failure. However, the treatment and the prognosis of KD associated with HPS is unclear. Our review of the literature revealed that KD associated with HPS in children seems to have a less aggressive course and a better prognosis than in adults (13). To our knowledge, HPS in a case of SS complicated with KD has not yet been reported in the English literature. Although the hemophagocytic lymphohistiocytosis (HLH)-94 and the HLH-2004 protocols of the Histiocyte Society recommend powerful treatments for HPS, including high-dose steroids, intravenous gamma globulin and an immunosuppressant agent, such as cyclosporine (14, 15), our patient recovered after receiving only moderate doses of oral prednisolone.

In conclusion, the findings from this case suggest that SS complicated with KD can be associated with the potentially fatal complication of HPS. The fact that the initial presentation of HPS in the patient was relatively mild might have contributed to the successful treatment. Although our experience is limited to this single patient, we postulate that exposure to certain viruses may induce the expression of RIG-I in epidermal cells as well as lymph node cells, thus triggering the activation of innate immunity.

The authors state that they have no Conflict of Interest (COI).

References