CASE REPORT

A unique case of IgG4-related skin disease and sclerosing cholangitis in a patient with previous hepatitis exposure

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INTRODUCTION

Immunoglobulin (IgG) 4-related disease (IgG4-RD) is an immune-mediated disorder of an unknown etiology characterized by the tissue infiltration of IgG4 plasma cells into affected organs. Thus far, IgG4-RD has largely been reported in the context of middle-aged Asian populations. Although IgG4-RD typically causes multiorgan involvement, IgG4-related skin disease is uncommon, occurring in only 4.2%-6.3% of cases. Among the cases of IgG4-related skin disease reported in the literature, cutaneous presentation seems to be categorized into 7 distinct morphologies (cutaneous plasmacytosis, pseudolymphoma and angiolymphoid hyperplasia with eosinophilia, Mikulicz disease, psoriasis-like eruption, unspecified macular, papular, or erythematous eruptions, hypergammaglobulinemic purpura and urticarial vasculitis, and ischemic digit). Although its pathophysiology is still under investigation, it is thought that the cutaneous manifestations of IgG4-RD occur because of IgG4 plasma cell infiltration, IgG4-directed inflammation, or a combination of the 2. IgG4-related skin disease is exceedingly rare and seldom presents concurrently with pancreaticobiliary involvement. We present a unique case of IgG4-RD with concomitant cutaneous and pancreaticobiliary involvement in a patient with previous hepatitis B exposure.

CASE REPORT

A 54-year-old Korean man with no significant medical history presented with epigastric pain, jaundice, and a pruritic rash. His laboratory parameters were remarkable for elevated levels of alanine aminotransferase (66 U/L), aspartate aminotransferase (50 U/L), alkaline phosphatase (179 IU/L), total bilirubin (21.9 mg/dL), direct bilirubin (16.3 mg/dL), and lipase (18 U/L). He was found to have positive serologies for hepatitis B core antibody but had a negative result for polymerase chain reaction for hepatitis B. Abdominal ultrasound revealed dilation of the intrahepatic and common bile ducts, without apparent stones. He underwent endoscopic retrograde cholangiopancreatography with sphincterotomy and stent placement to treat a distal common bile duct stricture. The endoscopic findings were significant for an enlarged and edematous pancreas, raising concerns for autoimmune pancreatitis. The biopsies of the ampulla of Vater and duodenum, however, were nondiagnostic.

His rash had persisted for 1 year and was unresponsive to topical steroid treatment. Physical examination was significant for ill-defined, erythematous eruptions, hyperpigmented thin plaques with secondary excoriations and lichenification. No oral, ocular, or anogenital involvement was present. The rash slightly improved following the biliary stent placement. A punch biopsy of the left side of the chest demonstrated a superficial and deep perivascular and periadnexal lymphoplasmacytic infiltrate with eosinophils throughout the dermis and extending into the subcutis. Immunohistochemistry demonstrated an increased IgG4:IgG ratio of 67% (Fig 2, C and D), fulfilling the histologic criteria for IgG4-RD (>40%); moreover, his corresponding IgG4 serum level was elevated at 448 mg/dL (<135 mg/dL), leading to a clinicopathologic diagnosis of IgG4-RD.
Fig 1. Ill-defined, erythematous to hyperpigmented thin plaques over the (A) anterior and (B) posterior aspects of the trunk.

Fig 2. A, B A punch biopsy of the left side of the chest shows a superficial and deep perivascular and periadnexal lymphoplasmacytic infiltrate with eosinophils throughout the dermis and extending into the subcutis. (A and B, Hematoxylin-eosin stain; original magnifications: A, ×4; B, ×20.) Immunohistochemistry for (C) IgG and (D) IgG4 demonstrate an increased IgG4:IgG ratio of 67%. (C and D, Hematoxylin-eosin stain; original magnifications: A, ×40; B, ×40.) IgG, Immunoglobulin.
The patient was initiated on prednisone at 40 mg (~0.6 mg/kg) daily, and he had significant improvement of his biliary obstruction and skin lesions; however, upon tapering over 1 month, his disease flared and he quickly became jaundiced, with significant worsening of his skin lesions. Given his glucocorticoid-dependent disease and the risk of long-term glucocorticoid toxicity, he was started on a combination therapy with rituximab and corticosteroid therapy based on evidence from small randomized trials.7,8 When remission was induced, the patient was begun on tapering prednisone combined with mycophenolate mofetil at 500 mg twice a day as a glucocorticoid-sparing agent, entecavir at 0.5 mg daily, and triamcinolone cream 0.1%. The patient had near-complete resolution of his skin lesions 8 weeks after his first rituximab infusion. Six months after starting the treatment, repeat laboratory parameters showed normalization of the serum IgG4 levels (50 mg/dL).

**DISCUSSION**

This case highlights an unusual presentation of a patient with IgG4-related skin disease with concurrent pancreaticobiliary involvement and a history of hepatitis B exposure. Currently, the pathophysiology of IgG4-RD is uncertain, and both genetic predisposition and environmental triggers are thought to prompt aberrant immune pathways to perpetuate the disease. Considering that hepatitis has been implicated in the pathogenesis of plasma cell dyscrasias,9,10 including an association with increased IgG4 levels,11 this patient’s IgG4 paraproteinemia may have been driven by subclinical viral activity and may explain, in part, why IgG4-RD is common in East Asia, where hepatitis B is more prevalent. We performed a PubMed search for all case reports with free full text available on “IgG4-related disease.” This resulted in 643 articles. Of those, only 81 cases reported having obtained viral serologies for hepatitis, and 14 cases (17%) reported having obtained positive hepatitis serologies, indicating past or current infection.

**Table I. Cases of IgG4-related disease with positive hepatitis serologies in the current literature**

| Case | Age (y) | Sex | Ethnic origin | Viral exposure | IgG4-related disease organ involvement |
|------|---------|-----|---------------|----------------|---------------------------------------|
| 112  | 64      | Male| East Asia     | Hepatitis B    | Autoimmune pancreatitis               |
| 212  | 65      | Male| Southeast Asia| Hepatitis B    | Sclerosing cholangitis, pancreatic lesions, and paraspinal lymphadenopathy |
| 313  | 56      | Male| Unknown       | Hepatitis B and C | Autoimmune hepatitis                   |
| 414  | 56      | Male| Unknown       | Hepatitis B    | Salivary glands, lymph nodes, skin, lungs, and liver Cholangitis and pancreatitis |
| 515  | 81      | Male| Unknown       | Hepatitis C    | Liver disease and pancreatitis         |
| 616  | 70      | Female| Unknown   | Hepatitis B    | Parotid gland                          |
| 717  | 37      | Male| Southeast Asia| Hepatitis B    | Ophthalmic, salivary glands, lacrimal glands, submandibular gland, lymphatic glands, and retroperitoneal fibrosis |
| 818  | 74      | Male| Unknown       | Hepatitis A    | Kidney                                 |
| 919  | 71      | Female| Unknown  | Hepatitis B    | Lung, mediastinal lymph nodes, and prostate |
| 1020 | 75      | Male| Unknown       | Hepatitis B    | Kidney                                 |
| 1121 | 55      | Male| Unknown       | Hepatitis B    | Pachymeningitis                        |
| 1222 | 49      | Male| Unknown       | Hepatitis B    | Bladder                                |
| 1323 | 71      | Male| Unknown       | Hepatitis C    | Retroperitoneal fibrosis and cholangitis |
| 1424 | 62      | Male| Unknown       | Hepatitis C    |                                        |

IgG, Immunoglobulin.

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**Conflicts of interest**

None disclosed.

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