Metachronous Multiple Clinical Presentations Involving the Skin in a Patient with Immunoglobulin G4–Related Sclerosing Disease

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Clinical Image

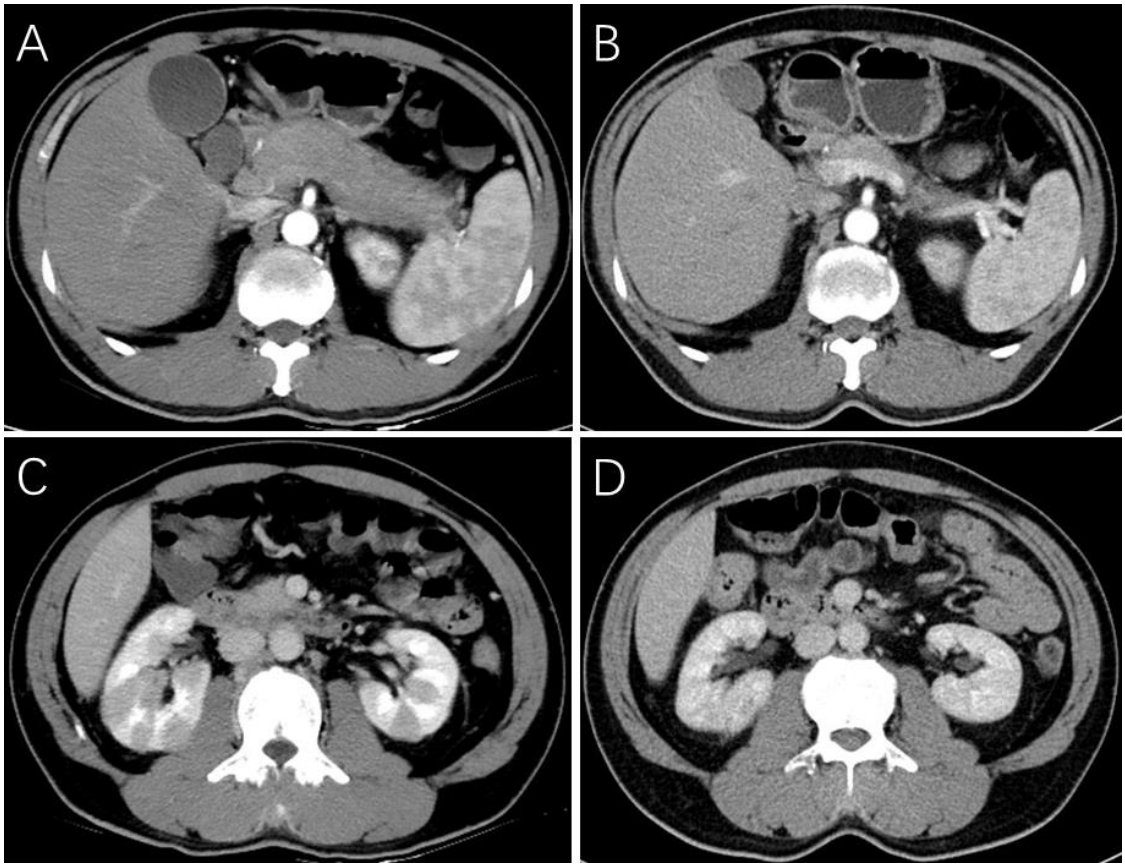

Figure 1: Contrast-enhanced abdominal computed tomography detecting characteristic sausage-like pancreas with a capsule-like low-density rim (A) and diffuse masses lacking of perfusion in bilateral kidneys (C), and significant improvement after hormonal therapy (B and D).

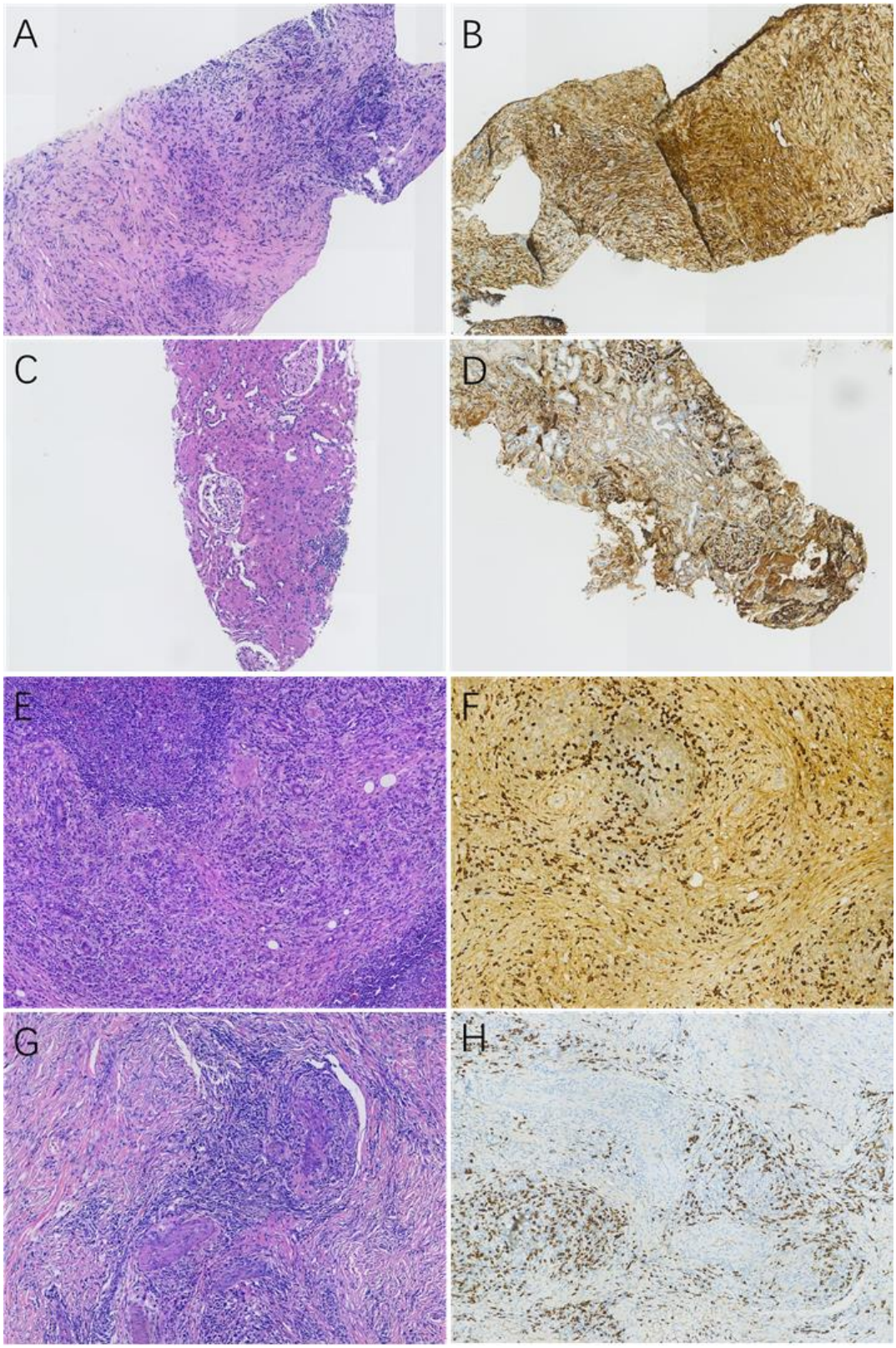

Figure 2: Pathological results showing storiform fibrosis, and extensive infiltration of lymphocytes and plasma cells with IgG4 deposition in pancreas (A, hematoxylin and eosin, and B, immunohistochemistry for IgG4), right kidney (C, hematoxylin and eosin, and D, immunohistochemistry for IgG4), right submandibular gland (E, hematoxylin and eosin, and F, immunohistochemistry for IgG4) and skin (G, hematoxylin and eosin, and H, immunohistochemistry for IgG4).

A 50-year-old male was admitted with yellowish urine for half month. His past history included resection of right submandibular gland in 2017 and dermatofibroma on the left upper limb in 2021. Physical examination revealed yellowing of the skin and sclera, and bilateral enlargement of inguinal and submandibular lymph nodes. On initial laboratory tests, liver enzyme levels were elevated (aspartate aminotransferase, 263.7U/L; alanine aminotransferase, 330.2U/L; gamma-glutamyl transpeptidase, 683 U/L; alkaline phosphatase, 343U/L), as well as total and direct bilirubin (46.8 umol/L and 25.9umol/L, respectively). Urinalysis identified urobilirubin (++), urobilinogen (+) and proteinuria (+). A full liver etiology screen was negative, with the exception of a weakly positive antinuclear antibody, and a polyclonal increase in gamma globulin (immunoglobulin (Ig) G, 58 g/L; immunoglobulin (Ig) E, 1050 IU/ml). Ultrasonography showed diffuse lesions in bilateral parotid glands and left submandibular gland with multiple hypoechoic nodules, and enlarged lymph nodes in bilateral groins. The contrast-enhanced abdominal computed tomography (CT) detected characteristic sausage-like pancreas with a capsule-like low-density rim (Fig. 1A), dilation of intra- and extra-hepatic bile ducts, and diffuse masses lacking of perfusion in bilateral kidneys (Fig. 1C). With symptomatic treatment, repeat tests showed slightly declines of the mentioned parameters. Therefore, the patient's medical histories were reviewed in detail and additional histopathological examinations of IgG- and IgG4-deposition in previous surgical specimens were taken, while the biopsies of pancreas and right kidney were conducted. The pathological results showed storiform fibrosis, and extensive infiltration of lymphocytes and plasma cells with IgG4 deposition (IgG4/IgG>50%) in pancreas (Fig. 2A and 2B) and right kidney (Fig. 2C and 2D), as well as in previous specimens from right submandibular gland (Fig. 2E and 2F) and skin (Fig. 2G and 2H), which were consistent with the histologic performance of IgG4 related disease (IgG4-RD). The elevated IgG4 (99.4 g/L) was also detected at the same time. Based on these findings, the diagnosis of IgG4-RD involving pancreas, kidneys, skin, parotid glands, submandibular glands and inguinal lymph nodes was made and prednisone was delivered with 50mg/day immediately. During prednisone taper-off at the outpatient clinic, azathioprine (100mg/day) was prescribed and maintained in consideration of the potential relapse. One month after discharge, urine routine and liver enzymes were restored to normal. Serum levels of IgG4 and IgE declined to 16.9g/L and 128 IU/ml, while IgG fell below the upper reference. Ultrasonography and abdominal CT reexaminations showed significant improvement of involved organs including pancreas (Fig. 1B), kidneys (Fig. 1D), etc. As a systemic autoimmune condition, IgG4-RD could cause fibro-inflammations in nearly all organs with distinctive IgG4-positive plasma cells infiltrated in lesions and the elevated serum IgG4 level in most patients and generally responses well to glucocorticoids (Peters *et al*., 2020), thus, correct identification of the disease is crucial. Reportedly, pancreato-biliary system was mostly involved but skin diseases were rarely observed (Lanzillotta *et al*., 2020). In our patient, pseudotumor as the single lesion in right submandibular gland was excised and remained remitted for the following four

years after resection without recognition of IgG4-RD. As the primary skin lesion prior to the systemic symptoms was rare and mostly appeared in head and neck (Charrow *et al*., 2016). Once again at this recurrence, cutaneous dermatofibroma wasn't initially identified as the primary symptom of IgG4-RD. Therefore, IgG4-RD should be fully considered and evaluated in clinical practices to avoid unnecessary and potentially harmful operations.

Keywords: *Immunoglobulin G4–Related Sclerosing Disease, Pancreas, Kidneys, Skin, Submandibular Glands*

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