IgG4-related disease: an uncommon cause of type 3c diabetes: a case report

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Introduction

Immunoglobulin (Ig)G4-related disease (IgG4-RD) is a chronic inflammatory immune-mediated condition that was recognised as a unified disease in 2003.[1] Its disease activity is associated with an increased number of immune cells, including B cells, plasma blasts and T cells (helper, regulatory and cytotoxic), in both the circulation and affected tissues, leading to fibrotic changes and possible organ damage.[2] The precise triggers underlying this chronic immune response remain undetermined. Although any organ may be involved, the pancreas, bile ducts, salivary glands and retroperitoneum are most frequently affected.[2] Pancreatic involvement may lead to diabetes, exocrine pancreatic insufficiency and pancreatitis.[1] Steroid treatment is the cornerstone of IgG4-RD management, and is most effective in the early inflammatory stages before fibrotic changes develop.[1]

Case report

A 51-year-old male presented to his GP with increased thirst and urination, blurred vision, and significant weight loss of 13 kg over two months. His capillary blood glucose was 28.6 mmol/L, urine ketones were 1+, his weight was 79 kg, and his BMI was 25.1 kg/m^2. His glycosylated haemoglobin (HbA_{1c}) was 129 mmol/mol, confirming the diagnosis of diabetes.

He was referred to the community diabetes team and urgently reviewed on the same day by the Diabetes Specialist Nurse. His capillary blood glucose level was 30 mmol/L, with a capillary ketone level of 0.4 mmol/L. He was commenced on basal insulin 16 units once daily in the morning, and the dose was gradually titrated upwards. Blood tests showed negative antibodies for glutamic acid decarboxylase (GAD65), zinc transporter 8 (ZnT8) and anti-tyrosine phosphatase-like insulinoma antigen 2 (IA-2), and his non-fasting C-peptide level was 304 pmol/L with a blood glucose of 11.9 mmol/L. A continuous glucose monitoring (Freestyle Libre) sensor was applied for continuous glucose monitoring. This indicated a need for short-acting insulin, so he was started on short-acting insulin with meals.

He was reviewed by the consultant to confirm the type of diabetes. It was noted that following insulin therapy, along with lifestyle and dietary modifications, his blood glucose improved significantly. Continuous glucose monitoring Freestyle Libre data over two weeks showed 69% time in target range (3.9–10 mmol/L), 30% above range (>10 mmol/L), and 1% below (<3.9 mmol/L). His weight stabilised, and the osmotic symptoms resolved.

Review of his past medical history revealed that he had presented to the ENT team 12 months earlier with a three-month history of dysphagia and a left submandibular swelling measuring 18 × 14 mm. Fine needle aspiration of the lesion showed reactive cells but could not exclude malignancy; excision of the lesion was performed. Histopathology revealed salivary gland tissue with lobular fibrosis, thick fibrous trabeculae and a prominent lymphoplasmacytic infiltrate. Acinar atrophy and storiform fibrosis were present, with more than 100 IgG4+ cells per high-power field and an IgG4:IgG ratio above 40%. These findings were consistent with IgG4-related sialadenitis.

The serum IgG4 level was normal at 0.91 g/L (reference range 0–1.3 g/L). Endoscopy was performed to investigate his dysphagia, and histopathology confirmed eosinophilic oesophagitis. He was managed with omeprazole 20 mg once daily and was referred to the immunology clinic for further management of IgG4-related disease. At the clinic he was started on prednisolone 40 mg daily, weaned by 10 mg every two weeks. Methotrexate was introduced to overlap with prednisolone before the latter was discontinued after four weeks.

Given his history of IgG4-related disease, the diabetes team arranged a CT scan of the pancreas, which demonstrated hypodense infiltrates around the liver capsule, splenic capsule

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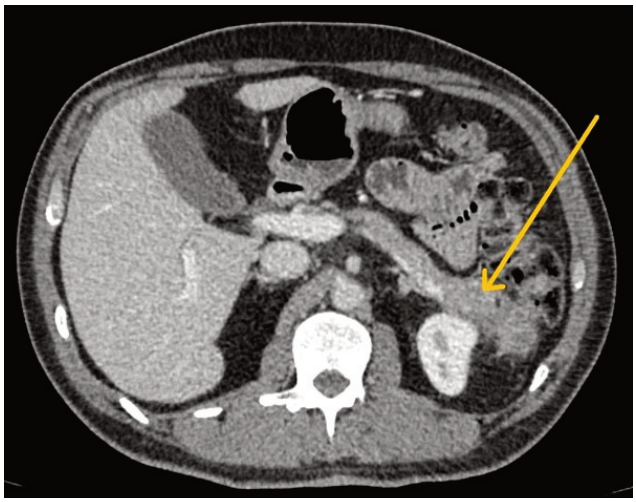
Figure 1. CT scan of Pancreas showing hypodense infiltrates of the pancreas with mild pancreatic atrophy



and pancreatic tail, along with mild pancreatic atrophy, but no calcification or mass lesions. These findings were consistent with IgG4 infiltration (Figure 1).

One year after diagnosis, his repeated non-fasting C-peptide level was 35 pmol/L with a paired blood glucose of 8.3 mmol/L, indicating total insulin deficiency. He was referred for diabetes education and attended a carbohydrate counting session. He maintained a good glycaemic target on a basal-bolus insulin regimen.

The acute presentation with osmotic symptoms, negative triple antibodies, rapid C-peptide decline and pancreatic infiltration on CT scan confirmed type 3c diabetes secondary to IgG4-mediated autoimmune disease.

At his latest review, the patient was very well and asymptomatic. He was on a basal bolus insulin regime with a total daily dose of 78 units. His average glucose was 8 mmol/L and his HbA_{1c} had improved to 52 mmol/mol. He remained clinically well on methotrexate 15 mg once weekly with folic acid 5 mg daily (six days per week). He was counselled on the risk of pancreatitis and symptoms of pancreatic exocrine insufficiency.

Discussion

This case highlights the importance of detailed history-taking, imaging and C-peptide monitoring to determine the type of diabetes. Unlike type 1 or type 2 diabetes (T1DM or T2DM), type 3c diabetes is caused by pancreatic disease such as chronic pancreatitis, pancreatic cancer, cystic fibrosis, hemochromatosis or surgical removal of the pancreas. Type 3c diabetes secondary to IgG4-RD is uncommon and may be misdiagnosed due to limited awareness of the condition. Early recognition is essential since management strategies differ from other diabetes types.

IgG4-RD is an immune-mediated inflammatory condition with unknown triggers; smoking is the only known modifiable risk factor.[3] Its prevalence is estimated at 5.3 per 100,000 persons, with an incidence of 1.4 per 100,000 person-years.[4] It typically affects individuals aged 50–60 years.[5]

Table 1. Diagnostic criteria for IgG4-RD.[10]

1.	Characteristic symptoms of organ infiltration (in the form of diffuse or tumourous enlargement) or organ disorder
2.	Elevated IgG4 levels in serum (>135 mg/dl)
3.	Lesions observed in histopathological tests:
	- Lymphoplasmacytic infiltration and fibrosis
	- Infiltration of IgG4-positive cells >10 IgG4-positive cells in the field of vision in a high definition microscope and with IgG4+/IgG ratio >40%
Diagnosis of IgG4-related disease:	
	- Certain 1 + 2 + 3
	- Probable 1 + 3
	- Likely 1 + 2

The disease involves antigen-driven interactions between B cells and CD4 T cells, including CD4-cytotoxic T lymphocytes and follicular helper T cells.[1] Multiple organ involvement occurs in around 60% of patients.[6] Symptoms are usually subacute, linked to organ enlargement from infiltration and fibrosis, but may also be discovered incidentally on imaging tests.[2]

IgG4-related endocrinopathies include Riedel's thyroiditis, IgG4-related Hashimoto thyroiditis, the fibrous variant of Hashimoto thyroiditis, Graves' disease with elevated IgG4, IgG4-related hypophysitis, and autoimmune pancreatitis (AIP).[6]

The first case of IgG4-RD was reported in 2001 in a patient with type 1 AIP and elevated IgG4.[7] AIP has two subtypes: type 1 (IgG4-related) is more common in Japan and Korea, while type 2 (with granulocytic epithelial lesions) is more prevalent in Europe and the USA.[8] AIP-related diabetes may develop at any stage.

Histopathology remains the gold standard for IgG4-RD diagnosis, and it helps to exclude other diagnosis such as malignancy, infection and vasculitis. The hallmark histopathology features are lymphoplasmacytic infiltration, fibrosis in storiform pattern and obliterative phlebitis.[1] Elevated serum IgG4 is present in 60–70% of patients,[6] and is useful in assessing disease activity, organ involvement, treatment response and relapse risk.[9] However, a normal IgG4 level does not exclude the diagnosis.[9] Serum IgE may be elevated in 50–90% of cases, and C3 and C4 levels may be low during active disease.[1]

Comprehensive diagnostic criteria for IgG4-RD were published in 2012 based on clinical, biochemical and histopathological features, categorising diagnoses as certain, probable or likely (see Table 1).[10] In this case, the IgG 4 level was normal, but the patient had evidence of salivary gland enlargement with infiltration of IgG4-positive cells and pancreatic dysfunction, with radiological features suggestive of IgG 4 infiltration. This case fulfils the diagnostic criteria for probable IgG4-related disease. The negative triple diabetes antibodies, salivary gland histopathology and pancreatic imaging findings supported the diagnosis of type 3c diabetes due to IgG4-RD.

Key messages

- IgG4-RD diagnosis requires clinical awareness, and management is best approached with an interprofessional team
- Patients with IgG4-RD should be screened for diabetes, particularly if pancreatic involvement is detected on imaging
- In patients with IgG4-RD and newly diagnosed diabetes, consider type 3c diabetes. CT scan of the pancreas and monitoring C-peptide levels are useful
- Glucocorticoids are most effective in the inflammatory phase of the disease, highlighting the importance of early diagnosis

Glucocorticoids are first-line therapy, followed by maintenance treatment with disease-modifying anti-rheumatic drugs (DMARDs) or biologics such as rituximab, with the goal of tapering glucocorticoids within 3–6 months.[1] In some cases, AIP-related hyperglycaemia may resolve with glucocorticoid therapy[11] However, steroid therapy may also worsen hyperglycaemia, necessitating insulin initiation. In this case, despite treatment with steroids and methotrexate, pancreatic fibrosis and atrophy led to complete insulin deficiency. This could be due to therapy not being introduced early enough following the diagnosis of IgG4-related sialadenitis and before the diagnosis of diabetes.

Our patient also had eosinophilic oesophagitis, a chronic immune-mediated condition causing dysphagia and reflux symptoms. Although distinct from IgG4-RD, recent research suggests a potential link.[12]

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