Rare disease

Unexplained refractory iron-deficiency anaemia in a 41-year-old woman

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Summary

The clinical and instrumental findings revealed a case of autoimmune polyendocrine syndrome (APS) type 3B+C in a 41-year-old Caucasian woman with unexplained refractory iron-deficiency anaemia secondary to autoimmune atrophic gastritis and a long-term history of two different autoimmune diseases—Hashimoto's disease and vitiligo. Indeed the occurrence in the same patient of three or more autoimmune diseases defines APS. The first classification of APS was suggested by Neufeld and Blizzard in 1980 and it included four main types of APS on the basis of clinical features. The only case of APS type 3B+C was described by Amerio *et al* in 2006.

BACKGROUND

Blood losses due to menstruation and haemorrhage are the most common cause of refractory iron-deficiency anaemia in a young woman. Atrophic autoimmune gastritis is also a potential, too often neglected, cause of iron-deficiency anaemia as the diagnosis of autoimmune polyendocrine syndrome (APS) in young patients with two or more autoimmune involvements.

We decided to present this case in order to offer some important clues to a complete diagnostic approach of iron-deficiency anaemia and to the diagnosis of APS. First, in the work-up of patients with unexplained iron-deficiency anaemia, an autoimmune origin for the anaemia should always be suspected. Second, in patients with specific autoimmune diseases of multiple non-endocrine and endocrine organs, an APS should always be considered.

CASE PRESENTATION

A 41-year-old Caucasian woman was admitted to our internal medicine ward for evaluation of a 6-year history of hypochromic, microcytic, iron-deficiency anaemia, which was unresponsive to oral iron supplementation and only partially responsive to parenteral iron administration. She also reported chronic fatigue. She had a 33-year history of generalised vitiligo, and subclinical hypothyroidism secondary to Hashimoto's disease had been discovered when she was 36-years-old. Menarche had occurred when she was 16-years-old. She reported regular menstrual periods (26–28 days) with menorrhagia. She had had two pregnancies; both delivered at term by caesarean section.

On admission, the patient was afebrile with a blood pressure of 120/80 mm Hg. The lungs were clear to auscultation and the heart sounds were normal except for a systolic murmur. She was 1.67 m tall and weighed 77 kg (body mass index 28). Examination of the skin revealed no signs of rash, but the breasts, trunk, arms and legs were covered with hypopigmented lesions that were consistent with the diagnosis of vitiligo vulgaris (figure 1). The neck displayed normal range of motion and no evidence of venous stasis.

Palpation revealed diffuse enlargement of the thyroid and left cervical lymphadenopathy.

The older of her two brothers also had generalised vitiligo, and the younger suffered from autoimmune thyroiditis. The patient was married and did not work outside the home. She denied smoking, alcohol consumption and use of all drugs (including aspirin and non-steroidal anti-inflammatory drugs).

INVESTIGATIONS

Laboratory data on admission revealed microcytic anaemia with normal iron values (haemoglobin 10.3 g/dl; haematocrit 31.2%; mean corpuscular volume 78 μm^3 ; iron 67 $\mu\text{g/dl}$), serum ferritin concentrations less than 25 ng/ml, transferrin saturation equal to 21% and a reticulocyte production index <2.5 (RI=0.343). Three stool samples were negative for occult blood. Endocrine and immunological tests revealed elevated serum levels of thyroid stimulating hormone, normal levels of free triiodothyronine and free thyroxine, and positive antithyroglobulin antibody titres. Ultrasonography of the neck confirmed the presence of chronic thyroiditis consistent with Hashimoto's thyroiditis (figure 2). Other blood tests were normal with the exception of raised gastrin (1151.0 pg/ml) and chromogranin A (250.9 ng/ml) levels, and positive titres of antigastric mucosa antibodies. Antiendomysium, anti-tissue transglutaminase and anti-gliadin antibody titres were negative.

Oesophagogastroduodenoscopy showed macroscopic features consistent with chronic atrophic gastritis and histological findings supported the diagnosis of atrophic chronic gastritis confined to the corpus-fundus with focal mucosa-associated lymphoid tissue (MALT) hyperplasia and no evidence of *Helicobacter pylori* infection (figure 3). Histological evidence of moderate chronic atrophic gastritis limited to the corpus and fundus in the presence of focal MALT hyperplasia, together with the results of endocrine and immunological tests (high gastrin and chromogranin A levels and the presence of antibodies directed against the gastric mucosa), were consistent with the diagnosis of autoimmune gastritis.

Figure 1 Generalised vitiligo characterised by bilateral and symmetrical distribution of the depigmented macules.

Figure 2 Ultrasonography of the neck confirmed the presence of chronic thyroiditis consistent with Hashimoto's thyroiditis.

Ileocolonoscopy, video capsule endoscopy and CT total body were all performed, without a source of bleeding or primary and metastatic neoplasia, inflammatory bowel disease, angiodysplasia and uterine abnormalities being identified.

DIFFERENTIAL DIAGNOSIS

The most important differential diagnoses taken into consideration were: (1) menorrhagia; (2) neoplasia, angiodysplasia and/or inflammatory disease of the gastrointestinal tract; (3) atrophic gastritis due to (a) chronic infection with

Figure 3 Lymphocytic infiltrates are present in the submucosa and lamina propria with clear signs of mucosa-associated lymphoid tissue hyperplasia.

H pylori, (b) autoimmune gastritis or (c) chronic high-dose treatment with proton pump inhibitors; (4) uterine abnormalities (such as fibroma, mioma or neoplasia) and (5) Hashimoto's thyroiditis with subclinical hypothyroidism.

TREATMENT

The patient received parenteral iron replacement once a week for 3 months.

OUTCOME AND FOLLOW-UP

After the first 2 months of treatment, the haemoglobin rose to 12 g/dl and the patient reported an improvement in her chronic fatigue. Iron replacement treatment was continued for another month after the anaemia had been corrected to replenish the patient's iron stores.

The patient is asymptomatic and the haemoglobin level remains stable after 6 and 12 months of follow-up.

DISCUSSION

Blood losses due to menstruation and haemorrhage are a common cause of iron-deficiency anaemia, and our patient's medical history included menorrhagia. Therefore, the initial diagnosis was microcytic anaemia due to iron deficiency with a subsequent cytoplasmic maturation defect and ineffective erythropoiesis.^{1 2} Our patient also had subclinical hypothyroidism, which leads to reduced thyroid hormone stimulation of the bone marrow and erythropoietin deficiency.³

However, our patient's iron-deficiency anaemia was refractory to supplemental iron and thyroxine treatment and only partially responsive to parenteral iron administration. Therefore, on the basis of the well-known major role played by gastric hydrochloric acid, we measured gastrin levels to investigate the state of the mucosa in the gastric corpus.

The finding of gastrin levels >100 pg/ml was compatible with a diagnosis of hypergastrinaemia—a condition frequently associated with the administration of histamine type-2 receptor antagonists or proton pump inhibitors, peptic ulcer disease, chronic gastritis (types A and B), gastric carcinoma without antral involvement, gastric carcinoid tumours (types 1 and 2), highly selective truncal vagotomy, Zollinger–Ellison syndrome, gastric-outlet obstruction, Billroth II gastrectomy with antral exclusion and massive small bowel resection.⁴ High plasma chromogranin A levels are also common in these conditions and in patients with neuroendocrine tumours (pheochromocytoma, oat-cell carcinoma of the lung, neuroblastoma, gastrointestinal and pancreatic tumours). Moreover, enterochromaffin-like cell hyperplasia secondary to hypergastrinaemia is a well-known cause of elevated blood levels of chromogranin A.

Our patient had no history of long-term treatment with proton pump inhibitors or histamine type-2 receptor antagonists, and she had never had surgery. Immunological tests revealed positive titres of antigastric mucosa

antibodies and the endoscopic evaluation supported the diagnosis of autoimmune gastritis. The normalisation of the haemoglobin level value with subcontinuous intravenous iron replacement confirms that the cause of the anaemia was impaired duodenal and proximal jejunal absorption secondary to hypochlorhydria caused by autoimmune gastritis. Dikey *et al*⁶ were the first to observe that autoimmune gastritis can present with iron-deficiency anaemia. Their findings were confirmed by Marignani *et al*⁶ and Annibale *et al* who observed that in 19.5–26% of patients with refractory iron-deficiency anaemia and no gastrointestinal symptoms the anaemia is caused by autoimmune gastritis.⁷ Therefore, in the work-up of patients with unexplained iron-deficiency anaemia an autoimmune origin for the anaemia should always be suspected. Moreover, in the presence of immune-mediated failure of non-endocrine organs (stomach, skin) and several endocrine glands (thyroid) we should always consider a rare polyendocrinopathy known as APS. In 1980, Neufeld and Blizzard distinguished four main types of APS on the basis of clinical features.⁸

APS-1 is an autosomal recessive disorder diagnosed during childhood or early adolescence and is caused by mutations of a single gene located on chromosome 21 (autoimmune regulator gene or *AIRE*). It is characterised by the presence of at least two of the following conditions: chronic candidiasis, chronic hypoparathyroidism and Addison's disease.⁹

APS-2 is an autosomal dominant disorder with incomplete penetrance and generally strikes women 20–40 years of age. Addison's disease is almost always present and is associated with autoimmune thyroid diseases and/or type 1 diabetes mellitus. APS-2 is associated with the HLA DR3/4 haplotype.

APS-3 is characterised by the presence of autoimmune thyroid disease (Hashimoto's thyroiditis, idiopathic myxedema, Graves' disease, asymptomatic thyroiditis or endocrine exophthalmus) and another autoimmune disease, excluding Addison's disease. Betterle and Zanchetta distinguish four subtypes (A, B, C and D) on the basis of the different organ-specific and non-organ-specific autoimmune disease associated, excluding Addison's disease and/or hypoparathyroidism.¹⁰ The only case of APS type 3B+C was described by Amerio *et al* in 2006.¹¹ It involved a 36-year-old woman with a 20-year history of generalised vitiligo, chronic autoimmune thyroiditis and autoimmune gastritis with high titres of antiparietal cell antibodies and pernicious anaemia.

APS-4 is a rare syndrome, which comprises all the clinical combinations not included in the other APS subtypes.

As for the pathogenesis of the APSs, it has been recently suggested that some external agents share one or more epitopes with an antigen common to several endocrine tissues (eg, those derived from the same germ layer).¹² Thus, exposure to such agents would trigger an autoimmune response directed against the germ-layer-specific antigen.

In conclusion, we believe that this case offers some important clues to the differential diagnosis and management of iron-deficiency anaemia and also to the identification of APS. First, in a premenopausal woman reporting menorrhagia, hypothyroidism and a history of refractory iron-deficiency anaemia—even if there are no gastrointestinal symptoms and fecal occult blood tests are negative—it

is important to consider gastrointestinal diseases that impair iron absorption, not only celiac disease and *H pylori* gastritis, but also less common conditions such as autoimmune involvement of the gastric corpus.¹³ Therefore, in the work-up of patients with unexplained iron-deficiency anaemia, screening for atrophic gastritis of the corpus based on measurement of gastrin and chromogranin levels and antigastric mucosa antibody titres might be carried out before the endoscopic biopsy procedure. Moreover, chronically high serum gastrin levels can cause the proliferation of enterochromaffin-like cells.^{14–16} Indeed, up to 10% of patients with autoimmune gastritis develop gastric carcinoid tumours or adenocarcinomas. Thus, regular gastroscopic surveillance should be offered to all patients with autoimmune gastritis.

Second, in patients with specific autoimmune disease of multiple non-endocrine organs (such as vitiligo, autoimmune gastritis, alopecia, celiac disease, rheumatoid arthritis, myasthenia gravis and pernicious anaemia), the possibility of multiple endocrine gland insufficiency (autoimmune thyroiditis, diabetes mellitus, Addison disease) should also be considered to exclude an APS. In contrast, patients with monoglandular endocrinopathies need to be screened for organ-specific autoantibodies to identify those at risk for developing APS in the future.

Learning points

- In the presence of chronic refractory iron-deficiency anaemia associated with a long-term history of two different autoimmune diseases, an autoimmune origin for the anaemia should always be suspected and investigated.
- All patients with autoimmune gastritis should undergo regular gastroscopic surveillance because of the risk to develop carcinoid tumours or adenocarcinomas (up to 10%).
- In patients with a single or multiple endocrine gland, insufficiency associated to an autoimmune disease of multiple non-endocrine organs should be considered to exclude an APS.

Competing interests None.

Patient consent Obtained.

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