CASE REPORT

Concomitant multiple myeloma, gastric adenocarcinoma and Evan's syndrome in a patient presenting with anaemia

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SUMMARY

An association between multiple myeloma (MM) and solid tumours has been previously described.¹ Furthermore, autoimmune disorders can precede plasma cell dyscrasias, and the pathogenesis of MM maybe linked to chronic immune stimulation.² We describe a case of concomitant MM and gastric adenocarcinoma preceded by Evan's syndrome. A previously healthy woman presented to the emergency room with symptomatic anaemia. Her initial workup was compatible with autoimmune haemolytic anaemia and monoclonal gammopathy of undetermined significance. On progression of the anaemia and development of thrombocytopenia, she was diagnosed with Evan's syndrome. Two months later, she presented with severe back pain and her MRI revealed L4–5 vertebral collapse. The clinical picture was compatible with MM. Occult blood was repeatedly positive in stools, and she underwent oesophagogastroduodenoscopy and was found to have gastric adenocarcinoma. The patient refused surgical resection of the adenocarcinoma and refused active treatment for MM.

BACKGROUND

Monoclonal gammopathy of undetermined significance (MGUS) is a known precursor of multiple myeloma (MM), with a risk of progression of 1% per year.³ MM represents 10% of haematological malignancies. Concomitant solid tumours and MM have been previously reported.¹

MM/MGUS has been associated with a range of autoimmune disorders including rheumatological, haematological and the neurological disorders.⁴ MM has been associated with autoimmune haemolytic anaemia (AIHA), thrombocytopenia and Evan's syndrome.⁴ The development of MM and gastric adenocarcinoma in this patient may have been associated with immune dysregulation.

CASE PRESENTATION

A 61-year-old, previously healthy, woman presented to the emergency room (ER) with shortness of breath, palpitations, dizziness and easy fatigability of 1 month duration. She denied weight loss or overt bleeding from any site, and her physical examination was unremarkable. She reported a history of passing black stool following ingestion of oral iron supplements. Her complete blood count showed haemoglobin (Hb) of 6.3 g/dL, MCV 105 fL, RDW 20%, platelets $168 \times 10^9/L$, reticulocytes of 9.2%, with a reticulocyte index of 1.6.

The patient was discharged from the ER and was given an appointment to the haematology clinic, where she was further evaluated. Her laboratory results showed low vitamin B₁₂ (22 pmol/L), and normal ferritin and increased total bilirubin (26 µmol/L), mainly indirect. (table 1) The patient was diagnosed with megaloblastic anaemia secondary to vitamin B₁₂ deficiency and started on parenteral vitamin B₁₂.

During her follow-up after 2 weeks, she showed modest clinical improvement and the Hb level was on average 8.0 g/dL.

She was lost to follow-up and presented 3 years later with evidence of microcytic anaemia, with a Hb value of 6.1 g/dL and low serum ferritin of 2.9 ng/mL. Following treatment with oral iron and parenteral vitamin B₁₂, her Hb showed only a mild improvement despite normalisation of vitamin B₁₂ and ferritin levels. The blood film showed evidence of haemolysis, and the direct Coomb's test (DCT) was positive with c3d specificity and LDH was elevated. On imaging, she was found to have splenomegaly and multiple gall bladder stones. As part of the investigation of anaemia in this age group, serum protein electrophoresis and immune fixation were ordered which showed a monoclonal IgG κ M component. The rest of the workup for plasma cell dyscrasias was negative, including a skeletal survey, 24-hour urine protein, urine Bence Jones proteins and a bone marrow aspirate and biopsy. On the basis of these findings, the patient was diagnosed with monoclonal gammopathy of undetermined significance (MGUS).

Six months later, she was seen in the haematology clinic and her physical examination revealed pallor and hepatosplenomegaly. Her ESR was elevated at 86 mm/H, and her counts showed a WCC of $2.18 \times 10^9/L$, Hb 9.5 g/dL and her platelets dropped to $73 \times 10^9/L$. The DCT remained positive for C3d, and her blood film showed signs of haemolysis and large platelets (figure 1). The diagnosis of Evan's syndrome was made based on these results, and she was started on prednisolone, tapered over the course of 3 weeks and both her haemoglobin level and platelet count improved.

Two months later, the patient started to complain of progressive back pain for which she was re-evaluated (table 2). The serum IgG M component was found to be 38.98 g/L, and B2-microglobulin was 4.98 mg/L. A bone marrow biopsy was repeated, and plasma cells were found to represent

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Table 1 The patient's investigations on initial presentation

Investigation (unit)	Result	Reference range
WCC (K/ μ L)	3	4.5–11.5
RBC (M/ μ L)	1.74	4.00–5.4
Hb (g/dL)	6.3	12–15
MCV (fL)	105	80–94
Platelets (K/ μ L)	168	150–450
RDW	20.4	
Reticulocytes (%)	9.2	
Vitamin B ₁₂ (pmol/L)	22.14	187–974
Ferritin (ng/mL)	78	30–400
Folate (nmol/L)	45	7–40
TSH (μ IU/L)	2.4	0.27–4.2
Total bilirubin (μ mol/L)	26	0–17
Direct bilirubin (μ mol/L)	3	0–5

hb, haemoglobin; WCC, white cell count.

Figure 1 The peripheral blood film showing rouleaux forms, polychromasia and large platelets.**Table 2** Results of MGUS workup

Investigations	Result	Reference range
WCC (K/ μ L)	2.18	4.5–11.5
RBC (M/ μ L)	3.28	4.00–5.4
Hb (g/dL)	9.5	12–15
MCV (fL)	90.2	80–94
Platelets (K/ μ L)	73	150–450
RDW	15.8	
Calcium (mmol/L)	2.02	2.1–2.52
Creatinine (μ mol/L)	52	53–115
IgG (g/L)	38.1	5.4–16.1
IgA (g/L)	2.18	0.8–2.8
IgM (g/L)	0.26	0.5–1.9
Immunofixation	IgG κ	
Bone marrow aspirate and biopsy	Monoclonal plasma cells represent 14% of nucleated bone marrow cells	
MRI	Vertebral collapse at L4–5 level	
Urine Bence Jones proteins	Negative	

MGUS, monoclonal gammopathy of undetermined significance.

14% of the nucleated bone marrow cells with an immunophenotype compatible with IgG MM, and κ light chain restriction. An MRI of her spine revealed vertebral collapse at the level of L4–L5.

Figure 2 (A) A large fungating gastric cardia mass with irregular borders as viewed by gastroscopy. (B) Pathology examination of the gastric mass revealed adenocarcinoma on a background of intestinal metaplasia.

Occult blood in stools was repeatedly positive, so she was planned for CT scan of the abdomen, esophagogastroduodenoscopy (EGD), colonoscopy and a coeliac screen. Tissue transglutaminase IgA was normal. Abdominal CT images showed a large, fungating gastric mass of 3.4×2.5 cm. Biopsy of the mass (figure 2A) revealed a well-differentiated gastric adenocarcinoma in the background of intestinal metaplasia (figure 2B).

The patient refused the recommendations of the surgical oncology team for resection of the adenocarcinoma and refused active treatment for MM. She discontinued oral steroids due to unwanted side effects.

She has been on supportive treatment for the past 18 months including vitamin B₁₂ injections, folic acid, oral iron supplement and proton pump inhibitors, with regular follow-up and monitoring of her blood counts.

DISCUSSION

Autoimmune disorders are associated with lymphoproliferative diseases.⁵ Recently, a systematic review reported on the strong association between autoimmune disease and MGUS/MM.⁶ AIHA is associated with 4–10% of cases of MGUS/MM, while the prevalence of Evan's syndrome in this patient population is largely unknown.⁴ Previously, Evan's syndrome preceded MM by 7 weeks in one patient⁷ and preceded gastric plasmacytoma by 7 years in another patient.⁸

A retrospective study found second primary malignancies in 4.5% of MM cases, of those 26.7% were gastric tumours.¹ Less commonly (35.7%), MM preceded primary second malignancies, similar to this case. Second primary gastric adenocarcinoma in the setting of IgG MM was reported in a 77-year-old man⁹ and a 68-year-old woman.¹⁰ Further, three cases of concomitant MM and gastric adenocarcinoma were reported in Japanese patients.^{11–13}

It is hypothesised that chemo-radiotherapy for treatment of MM is the likely culprit for the development of second primary malignancies,^{14–15} but in this case the patient received no treatment. Thus, other environmental or genetic factors may be implicated.

Autoimmune disorders are uncommonly described in association with solid tumours. Gastric adenocarcinoma was found on autopsy in a patient diagnosed with myasthenia gravis (MG), with concomitant Evan's syndrome.¹⁶ Another case of gastric cancer associated with warm AIHA.¹⁷ In both of these cases, the AIHA preceded the diagnosis of cancer by 2–8 years and responded to steroid therapy.¹⁷

Thus, autoimmune diseases are associated with haematological and solid malignancies, but Evan's syndrome is rarely reported in such an association. The aetiological link is yet undefined but chronic inflammation associated with autoimmune diseases may be at the heart of the underlying aetiology of clonal malignant disorders. Previous data suggest a shared

genetic susceptibility for MM and autoimmune disorders. Indeed, a causal link has been hypothesised between chronic immune stimulation and the development of haematological malignancies through the introduction of pro-oncogenic mutations in rapidly dividing haematopoietic cells.² Defective immune surveillance may lead to preselection of specific B-cell clones, which in turn heralds the progression to plasma cell dyscrasia.

Learning points

- ▶ Anaemia in the elderly needs to be evaluated adequately with a thorough history and physical examination, a complete blood count, red cell indices and a peripheral smear.
- ▶ An ESR test is also part of baseline anaemia workup in the elderly.
- ▶ A high MCV does not always mean megaloblastic anaemia (especially with a high reticulocyte count). If there is suggestion of haemolytic anaemia, workup with Coomb's test and further tests if needed.
- ▶ In elderly patients with bicytopenia, always evaluate thoroughly for causes of bone marrow infiltration. If initial marrow is normal, keep under close follow-up.
- ▶ Autoimmune cytopenia and other autoimmune phenomena may herald malignancy especially in elderly patients and warrant further investigation and follow-up.

Contributors MA-A contributed to the conception and drafting of the manuscript. SA contributed to the conception and drafting of the manuscript.

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