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CASE REPORT

Autoimmune haemolysis as an unusual cause of anaemia in von Recklinghausen's disease

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ABSTRACT

Von Recklinghausen's disease, now classified as neurofibromatosis type 1 (NF-1), is a relatively frequent autosomal dominant disorder and has clinical manifestations, such as cafe-au-lait spots, freckling, generalised cutaneus neurofibroma, Lisch nodules, short stature, optic glioma and central nervous system tumours. In adults, anaemia in the course of NF-1 is usually due to gastrointestinal tumour bleeding. Association of NF-1 and autoimmune haemolytic anaemia is unusual. Here, we report a 48-year-old woman with NF-1 presenting as autoimmune haemolytic anaemia. We also reviewed the literature about the association of NF-1 and autoimmune diseases.

INTRODUCTION

Neurofibromatosis type 1 (NF-1) is a common autosomal dominant neurocutaneus syndrome.[1] This syndrome is associated with a variety of benign and malignant tumours such as neurofibromas, neurofibrosarcomas, pheochromocytomas, central nervous system (CNS) tumours. In addition, children with NF-1 have increased risk for malignant myeloid disorders which may present with anaemia. However, in adults, there is insufficient data about the association of NF-1 and haematological malignancies. In adults, patients with NF-1 may present with anaemia due to bleeding from gastrointestinal tumours.[2-5] On the other hand, severe anaemia due to autoimmune haemolysis in NF-1 is unusual. We report a case of NF-1 presenting as autoimmune haemolytic anaemia with unexpected laboratory findings and dramatic response to oral prednisolone therapy.

CASE REPORT

The patient was a 48-year-old woman with NF-1 who had been taking oral iron preparations for anaemia for ten years. She was not taking any other medications. There was no information about previous laboratory tests since these tests were performed at another hospital ten years ago. Furthermore, the patient had not had any medical follow-up during the last ten years. She was referred to our hospital to examine the gastrointestinal tract as a source of iron loss. She had had no menstrual bleeding for four years. Medical history of the patient revealed no fever or weight loss suggesting lymphoma, no joint pain suggesting autoimmune disease, or no painful episodes suggesting sickle cell anaemia. Physical findings on admission were kyphosis and a short stature with a height of 140 cm and weight 43 kg. Blood pressure was 110/60 mmHg. There was no hepatosplenomegaly or lymphadenopathy. Cafe-au-lait spots, freckles and multiple soft skin tumours were observed over her entire body (*figure 1*). In addition, her daughter and three sisters had similar cutaneus physical findings.

The laboratory findings showed a reduction in red blood cells, haemoglobin, haematocrit, increase in reticulocytes, presence of normoblasts and normal mean corpuscular volume, lactate dehydrogenase (LDH), total bilirubin, unconjugated bilirubin (UB), iron, transferrin saturation and ferritin values (*table 1*). Liver and renal function tests were all within normal ranges. Levels of vitamin B12 and folic acid were in normal ranges. Haemoglobin electrophoresis was normal and no monoclonal gammapathy was detected in immunoelectrophoretic study. Direct Coombs' test was positive. Test for haptoglobin was not performed because of technical problems.

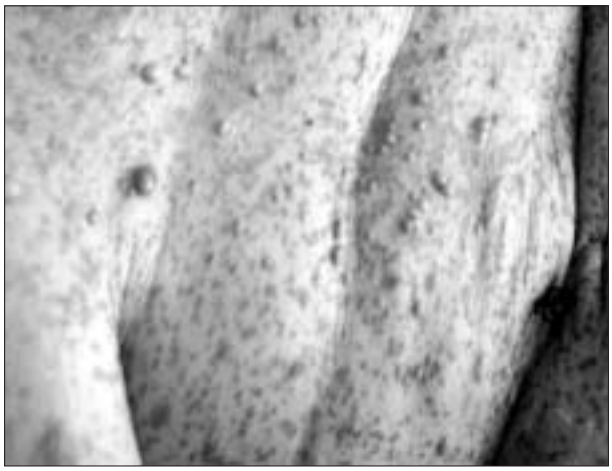

Figure 1
Cutaneus findings of abdominal region
Note the freckles and multiple soft skin tumours.

Table 1
Laboratory data on admission and 20th day of therapy

	ON ADMISSION	20TH DAY OF THERAPY
White blood cells	23.2 x 10^9/l	9.7 x 10^9/l
Red blood cells	1.96 x 10^{12}/l	4.38 x 10^{12}/l
Haemoglobin	2.5 mmol/l	7.6 mmol/l
Haematocrit	0.12 l/l	0.36 l/l
Mean corpuscular volume	81 fl	82 fl
Platelets	213 x 10^9/l	270 x 10^9/l
Iron (9-27 µmol/L)	11.7 µmol/l	14.0 mmol/l
Transferrin saturation	22%	25%
Ferritin (30-150 µg/L)	20 µg/l	28 µg/l
Reticulocytes	12%	2%
Corrected reticulocytes	4%	2%
Direct Coombs' test	positive	not performed
Normoblasts	6%	not seen
Peripheral blood smear	anisocytosis, polychromasia, spherocytosis, normoblasts	none
Lactate dehydrogenase	270 U/l (230-460 U/l)	310 U/l
Total bilirubin (5.1-17µmol/l)	4 µmol/l	3 µmol/l

Peripheral blood smear showed anisocytosis, polychromasia, normoblasts and spherocytosis. Infectious serologies including mycoplasma, hepatitis B, C, Cytomegalovirus, Ebstein-Barr virus and human immunodeficiency virus were negative. Tests for antinuclear antibody and anti-double-stranded DNA were also negative. Bone marrow examination was planned, but the patient refused it. Although laboratory findings were consistent with autoimmune haemolytic anaemia, normal values of LDH and UB were unexpected results. Furthermore, she had been anaemic for ten years. To exclude gastrointestinal bleeding, double-contrast barium studies of colon and small bowel, upper gastrointestinal endoscopy and rectosigmoidoscopy were performed and they revealed no gastrointestinal lesions. Angiography was not performed because of the absence of active gastrointestinal bleeding. Stool testing for occult blood was negative three times.

Abdominal ultrasonography revealed suspect hypoechogenic small lesions of the liver. Computed tomography as well as magnetic resonance imaging showed multiple, smaller than 1 cm, cystic lesions of the liver. We considered these lesions to be incidental since laparoscopy showed no liver surface lesions and biopsy revealed normal liver histology; these investigations were performed to exclude hepatic neurofibromatosis.

With the laboratory findings above, the diagnosis of autoimmune haemolytic anaemia was made and oral prednisolone was administered at a dose of 1 mg/kg. After 20 days, without any blood transfusions, all the haematological parameters were within the normal ranges (*table 1*).

DISCUSSION

NF-1, previously known as von Recklinhausen's disease, is a relatively common autosomal disease affecting one in 2190 to 7800 people.[6] The specific gene maps to chromosome 17q11.2.[7] Clinical manifestations of NF-1 include cafe-au-lait spots, freckling, generalised cutaneus neurofibroma, Lisch nodules, short stature, optic glioma and CNS tumours. NF-1 patients have increased risk of developing malignancies.[8] They have a high spontaneous mutation rate[1] and mutations in tumour suppressor genes play an important role in the development of tumours.[9] The most common cause of death is CNS tumours.[10]

The complication of gastrointestinal lesions has been reported in 25% of NF-1 patients.[11] When anaemia is seen in the course of NF-1, gastrointestinal system tumours have to be searched for carefully.[2-5] In some cases, only angiography was successful in identifying the focus of bleeding.[12,13] Bell *et al.*[14] reported an NF-1 patient with unexplained chronic anaemia for 21 years and finally diagnosed as retroperitoneal neurofibrosarcoma invading small intestine.

There are few reports of NF-1 patients associated with autoimmune diseases. Migita *et al.*[15] presented a case of

NF-1 associated with mixed connective tissue disease and treated with glucocorticoids. Scadding[16] reported the association of NF-1 with fibrosing alveolitis and autoimmune haemolysis. Toth *et al.*[17] presented an NF-1 patient with unexplained iron-deficient anaemia and secondary adrenal insufficiency who was successfully treated with glucocorticoids. The pathogenesis by which NF-1 is associated with autoimmune diseases is unknown. Gerosa *et al.*[18] reported that there were borderline levels of anti-DNA antibody and immune complex in some NF-1 patients. On the other hand, as with the present case, previously reported associations might be coincidental. There is insufficient evidence that autoimmune process plays a role in NF-1.

In our patient, although normal values of LDH and UB were inconsistent, positive direct Coombs' test and findings of peripheral blood smear brought us to the diagnosis of autoimmune haemolytic anaemia. The response to glucocorticoid administration was excellent without any blood transfusion which supported our diagnosis. An important point was that autoimmune haemolytic anaemia might be associated with haematological malignancies or autoimmune diseases. Although the patient was an adult, bone marrow examination was planned to exclude the diagnosis of myelodysplastic syndrome, but the patient refused it. Nevertheless, we considered that in addition to the age of the patient, dramatic response to glucocorticoid therapy was enough to exclude myelodysplastic syndrome. Lymphoma was excluded by the absence of fever, weight loss, organomegaly, or lympadenopathy. No monoclonal gammapathy was detected in immunoelectrophoretic study which strongly excluded multiple myeloma. An autoimmune disease was not considered since there were no clinical symptoms such as joint pain, weight loss or fever. In addition, antinuclear antibody testing was negative.

In conclusion, evaluation of anaemia in NF-1 patients seems to be difficult. While a careful search of the gastrointestinal tract is needed, it must also be borne in mind that NF-1 patients may present with autoimmune haemolytic anaemia. Furthermore, laboratory findings such as normal values of LDH and UB may not exclude autoimmune haemolysis.

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