

CASE REPORT

Cystic fibrosis presenting with haematological abnormalities

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Summary

Although cystic fibrosis (CF) is common, the diagnosis (and subsequent treatment) may be delayed if the presentation is atypical. We present three cases of children with CF who presented with haematological abnormalities. In all cases, they underwent extensive and invasive investigations prior to the diagnosis.

Keywords

Bone marrow, cystic fibrosis, haematology, stool elastase, sweat test

Case 1

Case 1 was born at term, weighing 3.45 kg (50th centile). She is the first child of healthy, non-consanguineous Albanian parents. She passed normal meconium on day 1 of life. She presented at 10 weeks of age with a persistent cough, loose green stools and failure to thrive. Pallor was the only abnormality on examination. Investigations confirmed a pancytopenia [haemoglobin 5.7 g/dl, white cell count $3 \times 10^9/l$, (neutrophils $1 \times 10^9/l$), platelets $31 \times 10^9/l$, MCV 84 fl, MCHC 35 g/dl, ferritin 480 ng/ml].

She was referred to the paediatric haematologists and underwent extensive investigations. Peripheral blood film, haemoglobin electrophoresis, haemolytic screen, autoantibody screen and bone marrow aspirate were all normal. Her symptoms improved and her pancytopenia resolved spontaneously without treatment over the following 2 months (haemoglobin 7.1 g/dl, white cell count $8 \times 10^9/l$, platelets $222 \times 10^9/l$). She presented at 10 months of age with fever, vomiting and frequent, loose, pale stools. There was no history of cough or respiratory symptoms. Her weight had dropped from 50th to 0.4th centile (6.6 kg). Sweat testing confirmed a

diagnosis of cystic fibrosis (CF; sweat chloride 85 mmol/l). Subsequent genetic testing confirmed her to be homozygous for the $\Delta F508$ gene. Faecal elastase was $<15 \mu g/g$ confirming pancreatic insufficiency. She was commenced on standard CF therapy. Her stool consistency normalized and she gained weight [14.3 kg (75th–91st centile) at 2 years of age].

Case 2

Case 2 was born at term, weighing 3.70 kg (50th centile). He is the first child of healthy, non-consanguineous Caucasian parents. He had pale, frequent stools from birth. He presented at 10 weeks of age with vomiting diarrhoea, poor weight gain (dropped to 10th centile) and severe nappy rash. Examination revealed a pale, underweight child with severe perineal rash. Investigations showed haemoglobin 6.8 g/dl, white cell count $11.6 \times 10^9/l$, platelets $393 \times 10^9/l$, albumin 16 g/l. He was referred to the paediatric haematologists for further investigation of his profound anaemia. His reticulocyte count was 2.8%, but an extensive haemolytic screen was all normal. Iron studies suggested significant iron overload (serum iron 30.2, transferrin saturation index 190%). This together with the low reticulocyte count suggested a problem with red blood cell production. He was transfused and underwent bone marrow aspiration and trephine. This confirmed reasonable cellular bone marrow but with an excess of vacuolated precursors. Some also had siderotic granules

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on iron staining. There was no abnormal blast infiltration. The combination of failure to thrive, gastrointestinal symptoms, hypoalbuminaemia and vacuolated precursors on bone marrow suggested a diagnosis of Pearson's syndrome (Alter, 2002) and he was referred to the paediatric gastroenterologists. Mitochondrial DNA analysis was subsequently normal.

He represented at 4 months with ongoing diarrhoea and vomiting, poor weight gain and persisting napkin rash. There was no history of cough or respiratory symptoms. Examination revealed an unwell child with pallor and irritability, severe peripheral oedema and hepatomegaly. Weight was 5.13 kg (second centile). Investigations showed haemoglobin 9.9 g/dl, white cell count $22 \times 10^9/l$, platelets $178 \times 10^9/l$, bilirubin 24 $\mu\text{mol/l}$, alanine aminotransferase 95 U/l, albumin 11 g/l. Serum zinc and copper levels were normal. He was commenced on hydrolysed feeds but continued to have frequent loose green stools. He was treated with 20% albumin and leucocyte-depleted blood transfusions. He then developed a *Staphylococcal* pneumonia. A sweat test confirmed a diagnosis of CF (sweat chloride 130 mmol/l). Subsequent genotyping confirmed him to be homozygous for the $\Delta F508$ gene and pancreatic insufficient (stool elastase $<15 \mu\text{g/g}$). He was transferred to a tertiary paediatric respiratory centre, commenced on pancreatic enzyme replacement therapy and received 2 weeks of intravenous antibiotics. He was re-established on breast-feeds and solids and subsequently thrived [12.16 kg (25th–50th centile) at 2 years of age].

Case 3

Case 3 was born at 36 weeks gestation and weighed 3.0 kg (25th centile). He was the first child of healthy, consanguineous (first cousin) Kuwaiti parents. He fed poorly from birth and presented at 2 months of age with vomiting and poor weight gain. Examination revealed marked pallor and oedema of the lower limbs. Admission haemoglobin was 5.2 g/dl (reticulocytes 3.9%) and albumin was 17.1 g/l. A bone marrow aspirate showed erythroid hypoplasia suggesting a diagnosis of red cell aplasia. He was transfused and referred to the paediatric haematologists. He underwent a repeat bone marrow examination, which confirmed a cellular marrow, active and normoblastic erythropoiesis and active myelopoiesis. Seven per cent blast cells were seen. A diagnosis of refractory anaemia with excess blast cells was made. A third bone marrow 3 weeks later was normal and his profound anaemia and hypoalbuminaemia completely resolved.

He was re-admitted at 4 months of age with a paroxysmal cough. During one of these paroxysms, he developed a pneumomediastinum with surgical emphysema of his neck and chest wall. He was admitted to the paediatric intensive care unit and treated supportively. He had an ongoing cough and respiratory distress and a sweat test confirmed a diagnosis of CF (sweat chloride 121 mmol/l). Despite extended genetic testing, a gene deletion has not been identified in this patient. Stool elastase confirmed pancreatic insufficiency. He was commenced on standard CF therapy following which his respiratory symptoms improved and he gained weight [8.6 kg (25th centile) at 1 year].

Discussion

Haematological abnormalities are well recognized in patients with CF. Anaemia has been described in relation to the nutritional and haematinic deficiencies associated with CF and secondary to treatment given in established disease. For example, haemolytic anaemia, leucopenia and thrombocytopenia have all been reported in association with piperacillin treatment (Reichardt *et al.*, 1999; Thickett *et al.*, 1999). In addition, profound anaemia is not uncommon in patients with established CF. However, the frequency of clinically significant anaemia at presentation in infants with CF is much lower (estimated to be 4–5%; Nielsen & Larsen, 1982; Wilfond *et al.*, 1994). In all three cases, significant anaemia was a feature at presentation.

Whilst the pathogenesis of early anaemia in CF has not been conclusively established, a number of factors have been implicated in contributing to the development of severe anaemia. These include anaemia of chronic disease and maldigestion secondary to pancreatic exocrine dysfunction (Kahre *et al.*, 2004). Most studies describe the anaemia as haemolytic, implicating the malabsorption of fat-soluble vitamin E (Farrell *et al.*, 1993; Wilfond *et al.*, 1994; Savasan *et al.*, 1997; Swann & Kendra, 1998). There is evidence that vitamin E deficiency can cause haemolysis because of increased susceptibility of the erythrocyte membrane to oxidant stress (in the absence of antioxidant vitamin E, free radicals are generated that result in peroxidation of the lipid components of the red cell membrane and subsequent reduced red cell survival; Oski & Barnes, 1967; Farrell *et al.*, 1977). Additionally, there are reports of correction of haematological indices and *in vitro* haemolysis with the administration of exogenous vitamin E (Monzon & Woodruff, 1986; Kelleher *et al.*, 1987). The frequency of vitamin E deficiency in infants with newly diagnosed CF is very high (38–59%; Sokol *et al.*, 1989; Marcus *et al.*, 1991). The underlying

mechanism for this is not understood. It has been shown to be independent of exocrine pancreatic function (Lancellotti *et al.*, 1996) and administration of pancreatic enzymes has been demonstrated not to correct the vitamin E deficiency (Sinaasappel *et al.*, 2002). Both of these facts suggest that it is not exocrine pancreatic insufficiency alone that is responsible for the development of vitamin E deficiency. Despite the reported frequency of vitamin E deficiency in newly diagnosed CF, only a small minority will have clinically significant anaemia. This suggests that other factors are involved in the development of severe anaemia in CF.

A proportion of children will have anaemia as part of a symptom complex of protein-energy malnutrition (PEM; anaemia, hypoproteinaemia and oedema (Shahidi *et al.*, 1961; Dolan, Rowe & Bibson, 1970; Lee, Roloff & Howatt, 1974; Dolan, 1976; Muniz, Bartle & Foster, 2004). This group accounts for 3–13% of patients presenting with CF (Nielsen & Larsen, 1982; Abman, Accurso & Bowman, 1986). The anaemia associated with PEM has been reported as primarily normocytic normochromic (Shahidi *et al.*, 1961; Bass & Miller, 1977). Earlier case series suggest the anaemia is associated with reduced serum iron levels and total iron-binding capacity (Lahey *et al.*, 1958; Shahidi *et al.*, 1961; Ater *et al.*, 1983; Savasan *et al.*, 1997). Hypoproteinaemia is thought to result in reduced levels of iron-binding globulin and subsequent inadequate mobilization and transport of iron. A more recent case series, however, reports normal serum iron levels in three of the four patients in whom it was measured (Nielsen and Larsen 1982). Serum haemoglobin levels rise with exogenous iron as the protein concentration rises (Lee, Roloff & Howatt, 1974). PEM has historically always been associated with severe disease progression and a high morbidity and mortality (Fleisher *et al.*, 1964; Abman *et al.*, 1985; Abman, Accurso & Bowman, 1986). In the first case series reported in the literature, one-third died during the period of oedema and less than half survived for longer than 2 months (Fleisher *et al.*, 1964). A more recent paper reported seven infants with PEM all of whom survived (Nielsen and Larsen 1982). This is likely to be because of earlier recognition and awareness of the diagnosis. However, there remains a significant burden of severe pulmonary complications in these children. All reported cases are pancreatic insufficient. Most of the case series predate CF genetic testing and there is only one report of a confirmed genotype in a child with CF presenting with PEM (Kahre *et al.*, 2004).

The literature on other haematological abnormalities at presentation in patients with CF is very limited. To our knowledge, case 1 represents the first report of a child with

CF presenting with pancytopenia. The mechanism for this remains completely obscure. All three cases we present underwent bone marrow examination. To date, there have only been a small number of previous case reports of bone marrow abnormalities in children with CF presenting with severe anaemia and PEM. Three cases were reported as showed erythroid hypoplasia (as in case 2; Shahidi *et al.*, 1961; Phillips *et al.*, 1993). This was associated with dyserythropoiesis with vacuolated cytoplasm in one child (Phillips *et al.*, 1993). To date a single case has been reported as having (moderate) myelodysplastic changes (Kratz *et al.*, 2004). Case 3 represents a second similar case, which fulfils the criteria for childhood myelodysplastic syndrome (Hasle *et al.*, 2003). There have only been two other cases in the literature of infants with CF and anaemia receiving a bone marrow aspiration. One was reported as normal (Worley, Poole & Valdes-Depena, 1979) and one showed marked left shift of myelopoiesis (Farrell *et al.*, 1993).

While CF presenting with profound abnormalities in haematological parameters is relatively uncommon, it is important to consider the diagnosis in patients with an appropriate clinical presentation. In all three of these cases, children underwent extensive and invasive investigations leading to a delay in the diagnosis and treatment of their CF. A sweat test is a simple, non-invasive test that should be performed early in children presenting with a suspicious history and haematological abnormalities. We further suggest that a selected group of patients confirmed to have CF on a positive sweat test may warrant a trial of treatment to assess any improvement in clinical and haematological parameters, prior to performing a bone marrow examination.

Conflict of interest

No conflict of interest.

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