Case Report

Diagnosis of Fanconi Anaemia in child with massive pulmonary embolism: case report and literature review

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Abstract

Fanconi anaemia is a rare inherited syndrome characterised by bone marrow failure, congenital anomalies and predisposition to malignancy. We report the case of a teenager who presented with massive pulmonary embolism and persistent moderate cytopenia. His biological work-up revealed an abnormal chromosomal break leading to the diagnosis of Fanconi anaemia and antithrombin III deficiency. Despite the presence of other promoting factors, we discuss whether the risk of thromboembolic events might be increased in patients with congenital or acquired aplastic anaemia.

Introduction

Fanconi anaemia (FA) is a rare inherited (mainly autosomal recessive) disorder characterised by congenital abnormalities, progressive bone marrow failure, and a predisposition to malignancy. FA is caused by mutations in the *FANC* family of genes, which encode for proteins involved in desoxyribonucleic acid (DNA) repair, leading to genomic instability. The most frequently mutated genes are *FANCA*, *FANCC* and *FANCG* (1).

Congenital malformations are the most common presenting features. They typically include skin findings like café-au-lait spots, short stature, thumb or other radial ray abnormalities, axial skeletal malformations, congenital heart disease and genitourinary, renal, gastrointestinal, central nervous system, ear, and eye abnormalities. Haematological manifestations include thrombocytopenia, macrocytic anaemia or pancytopenia due to progressive bone marrow failure. Myelodysplastic syndromes (MDS), acute myeloid leukaemia and squamous cell carcinoma of skin, head, neck and tongue are among the malignancies that are increased in patients with FA (1).

FA is usually diagnosed in the first decade of life. However, recent studies on large registries supported by genetic analysis have shown a wide spectrum of clinical presentation with diagnosis sometimes delayed into adulthood (1).

We report the clinical history of a teenager who presented with massive pulmonary embolism (PE). Careful examination revealed discrete phenotypic abnormalities and persistent moderate cytopenia suggesting the diagnosis of FA. This observation was consistent with other reports describing an increase of venous thromboembolism (VTE) in patients with acquired or congenital aplastic anaemia (AA) (2-5).

Case reports

A 15-year-old boy was initially treated for right pneumonia. Biology showed an inflammatory syndrome (C-reactive protein 149 mg/L [N <5]), aregenerative macrocytic anaemia (haemoglobin: 10.5g/dl [N 11-14.3], MCV: 104 fL [N 81-87], reticulocytes: 44*10^{e}3/mm^3 [N 39-100]) with normal folic acid and vitamin B12, normoleukocytosis (WBC: 5.21*10^{e}3/mm^3 [N 5.2-9.7], neutrophils: 2.77*10^{e}3/mm^3 [N 2.7-6.7]) and thrombocytopenia (platelets: 71*10^{e}3/mm^3 [N 180-299]). He clinically improved after antibiotherapy and biological evolution showed a decrease of the inflammatory syndrome but persistence of macrocytic anaemia (haemoglobin: 9.7 g/dl, MCV: 104 Fl), thrombocytopenia (platelets: 66*10^{e}3/mm^3) and appearance of a mild neutropenia at 1.26*10^{e}3/mm^3 (Table 1).

Two months later, after a four-hour bus journey, the child presented with acute dyspnoea and chest oppression. Blood tests showed macrocytosis without anaemia (haemoglobin: 14.4g/dl, MCV: 105fl), normal leukocytosis (WBC: 6.62*10^{e}3/mm^3), thrombocytopenia (platelets: 40*10^{e}3/mm^3), and no inflammatory syndrome (Table 1). He rapidly progressed to hypoxemic respiratory failure and obstructive shock. Computed tomography pulmonary angiography showed a massive bilateral pulmonary embolism (PE). The patient was treated urgently with surgical thrombectomy with sternotomy (thrombocytopenia contraindicated thrombolysis) followed by anticoagulation with enoxaparin. Doppler examination of the lower limbs revealed no deep vein thrombosis (DVT). The respiratory condition improved rapidly but biological abnormalities such as thrombocytopenia (platelets: between 49 and 53*10e3/mm^3) and macrocytosis (MCV: between 103 and 128 fL) persisted with the progressive onset of moderate leukopenia (WBC: 3.01*10^{e}3/mm^3) and anaemia (haemoglobin: 7.1 g/dl) (Table 1).

The initial coagulation work-up was normal (before anticoagulant treatment): INR 1.15, ACT (activated cephalin time) 34 seconds (N 25-42), C and S protein levels at 105% and 93% respectively (N 70-130%). Lupus anticoagulant and antiphospholipid tests were negative. Thorough thrombophilia evaluation revealed antithrombin III (ATIII) deficiency with repeated levels between 50 and 60 % and serum homocysteine levels at the upper limit of normal (11 µmol/L for a standard between 4 and 10). Low ATIII levels were also found in the patient's mother and two sisters, suggesting a familial deficiency. Genetic workup revealed no factor V LEIDEN mutation or factor II mutation.

Several clinical features were noted in the context of moderate cytopenia: small size (height: 156cm, (< 5th percentile), triangular face, hypotelorism, subtle hypotrophy of the thenar eminence and an increase in foetal haemoglobin to 8.5% (N < 2%). Medullary puncture showed moderate hypoplasia without myelodysplasia or clonal abnormalities. The mitomycin C test showed an increase in chromosomal breakages, suggesting the diagnosis of FA. Molecular analysis confirmed that the patient was a heterozygous carrier of 2 deletions of the *FANCA* gene. Morphological examination revealed no other cardiac, renal or bone abnormalities.

The patient was anticoagulated with dabigatran. He required 2 red blood cell transfusions and is currently being considered for unrelated hematopoietic cell transplantation. Anticoagulation will need to be maintained throughout the transplantation.

Discussion

FA is a genetically and phenotypically heterogeneous disorder. A large study analysing data from the International Fanconi Anaemia Registry (IFAR) has shown that approximately one third of patients have no major congenital malformations. In these patients, diagnosis is usually delayed and made after the occurrence of haematological dysfunction (1). Similarly, investigations in children and young adults have suggested that genetic screening should be considered in all patients presenting AA or MDS even in the absence of familial history or physical abnormality (6). Our patient displayed discrete dysmorphic signs and short stature but the FA diagnosis was finally evoked in the context of PE, revealing persistent macrocytic aregenerative anaemia and moderate thrombocytopenia.

PE is rare in children. It has a bimodal distribution with higher incidence in infants and adolescents. The Canadian and Dutch registries report incidence rates of VTE - which includes both DVT and PE - of 0.07 to 0.14 per 10,000 children (7). In paediatrics, the main risk factors for VTE are central venous catheters, hereditary thrombophilia, immobility, inflammatory conditions such as systemic infections or inflammatory diseases, haematological malignancies, solid cancers, trauma, surgery, use of hormonal contraceptives and nephrotic syndromes. More than 95% of children with VTE have at least one underlying clinical condition (7).

Several factors may have favoured PE in our patient. First, the repeated low ATIII levels observed were consistent with an inherited deficiency. Inherited ATIII deficiency is an autosomal dominant disorder caused by a mutation in the *SERPINC1* gene that results in a reduction in AT levels of between 40 and 60% (type I) or functionally defective AT (type II). Although we do not have genetic confirmation, the reduced levels measured in the patient and several family members suggest a hereditary AT III type I deficiency.

Second, venous stasis resulting from 4 hours of immobilisation during the bus journey may also have promoted thromboembolism. In a systematic review, Rajpurkar and colleagues reported a prevalence of immobilisation of 38% in paediatric patients with PE (62 out of 163 patients) (8). In our patient, echo doppler of the lower limb showed no DVT. In large series, only 30 to 60% of patients with PE associated with immobilisation have DVT (7).

A previous pulmonary infection may also have contributed to the PE in our patient. By increasing blood coagulability and venous stasis, infection and subsequent inflammation are known to promote thromboembolism. This risk of VTE increases 2-4-fold following respiratory infection, and the association is strongest in the first 2 weeks after the onset of infection, with a gradual decline thereafter (9).

Finally, we wondered whether the diagnosis of FA in our patient was merely coincidental or whether it might have played a role in the development of PE in addition of other risk factors. A prospective comparative study has shown a 2.5-fold higher incidence of VTE in patients with AA compared with non-AA patients. This study involved mainly adult patients (with only 24% of subjects under 49 years of age) treated exclusively for secondary and idiopathic AA (5). VTE has also been reported in children and young adults with inherited AA such as Blackfan-Diamond syndrome. Several risk factors have been identified in these cases: central venous catheters, treatment with interleukin-3 for Blackfan-Diamond anaemia, and snakebite in a patient with iron overload induced by repeated transfusions (2-4). These observations do not exclude a role of immune dysregulation and altered haematopoiesis in promoting VTE in AA. Pro-inflammatory cytokines namely tumour necrosis factor alpha (TNFα), interleukin 6, and interleukin 2 contribute to the pathogenesis of bone marrow failure in AA. TNFα also induces the production of reactive oxygen species and the activation of several transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa B). In addition, NF-kappa B plays a role in vascular smooth muscle cell growth, vascular remodelling, atherogenesis, and VTE (5). A potential link between FA and thromboembolism has also been supported by a recent animal model of FA. Raman and colleagues reported that *FANCA*-/- and *FANCO*-/- zebrafish had a shortened venous time to occlusion. They hypothesised that erythrocyte lysis due to complement, as observed in aplastic anaemia, may promote this thrombotic feature (10).

Conclusion

To our knowledge, this is the first report of PE in a patient with FA. There is insufficient evidence to confirm a link between the two diseases. However, a review of the scientific literature revealed some interesting observations. In addition to ATIII deficiency and immobilisation, the prothrombogenic immune changes associated with bone marrow failure and the recent pulmonary infection may have favoured the occurrence of VTE in our patient.

This report also highlights the importance of considering the diagnosis of congenital aplastic anaemia when faced with unexplained persistent cytopenia in children, adolescents and young adults, even in the absence of an obvious congenital abnormality.

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Table 1: Laboratory examination at the first admission with pneumonia, two months later at the second admission with pulmonary embolism and during the follow-up.

Parameters, Normal Values	Day 0 Pneumonia	*Day 10*	*Day 60 Pulmonary embolism*	*Day 66 Post- thrombectomy*	Day 150 Follow-up
Haemoglobin, 11.0-14.3 g/dL	10.5	9.7	14.4	10.1	7.1
MCV, 81-87 fL	104	104	105	103	128
Reticulocyte, 39-100 $10^e3/mm^3$	44		11	97	200
Total leukocyte count, 5.2-9.7 $10^e3/mm^3$	5.21	4.66	6.62	4.42	3.01
Neutrophil count, 2.7-6.7 $10^e3/mm^3$	2.77	1.26	5.73	1.7	1.37
Platelet count, 180-299 $10^e3/mm^3$	71	66	40	49	53
CRP, <5 mg/L	150	16	7		

MCV = mean cell volume; CRP = C-reactive protein.

Disclosure statement

All authors declare that they have no conflicts of interest.

REFERENCES

1. Auerbach AD. Fanconi anemia and its diagnosis. Mutat Res. 2009;668(1-2):4-10.
2. Norris ML, Klaassen R. Central venous catheter thrombosis as a cause of SVC obstruction and cardiac tamponade in a patient with Diamond-Blackfan anemia and iron overload. Pediatr Blood Cancer. 2006;46(1):112-4.
3. Gillio AP, Faulkner LB, Alter BP, Reilly L, Klafter R, Heller G, et al. Treatment of Diamond-Blackfan anemia with recombinant human interleukin-3. Blood. 1993;82(3):744-51.
4. Makis A, Kattamis A, Grammeniatis V, Sihlimiri P, Kotsonis H, Iliadis A, et al. Pulmonary embolism after snake bite in a child with Diamond-Blackfan anemia. J Pediatr Hematol Oncol. 2011;33(1):68-70.
5. Lin CL, Lin CL, Tzeng SL, Chung WS. Aplastic anemia and risk of deep vein thrombosis and pulmonary embolism: A nationwide cohort study. Thromb Res. 2017;149:70-5.
6. Keel SB, Scott A, Sanchez-Bonilla M, Ho PA, Gulsuner S, Pritchard CC, et al. Genetic features of myelodysplastic syndrome and aplastic anemia in pediatric and young adult patients. Haematologica. 2016;101(11):1343-50.
7. Ramiz S, Rajpurkar M. Pulmonary Embolism in Children. Pediatr Clin North Am. 2018;65(3):495-507.
8. Rajpurkar M, Biss T, Amankwah EK, Martinez D, Williams S, Van Ommen CH, et al. Pulmonary embolism and in situ pulmonary artery thrombosis in paediatrics. A systematic review. Thromb Haemost. 2017;117(6):1199-207.
9. Cha SI, Choi KJ, Shin KM, Lim JK, Yoo SS, Lee J, et al. Clinical characteristics of pulmonary embolism with concomitant pneumonia. Blood Coagul Fibrinolysis. 2016;27(3):281-6.
10. Raman R, Ramanagoudr-Bhojappa R, Dhinoja S, Ramaswami M, Carrington B, Jagadeeswaran P, et al. Pancytopenia and thrombosis defects in zebrafish mutants of Fanconi anemia genes. Blood Cells Mol Dis. 2022;93:102640.