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Brief Report

Atrioventricular septal defect in a case of Shwachman–Diamond syndrome

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Abstract Shwachman–Diamond syndrome is an inherited bone marrow failure and cancer predisposition syndrome that affects multiple organ systems, including bone, pancreas, and, to a lesser extent, the heart. Myocardial fibrosis, necrosis, and a case of dilated cardiomyopathy have, so far, been described. We report the first case of atrioventricular septal defect in a patient with Shwachman–Diamond syndrome.

Keywords: Shwachman–Diamond syndrome; atrioventricular septal defect; congenital heart disease; neutropaenia

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Case presentation

A 22-year-old woman was referred to our Haematology Unit because of bicytopaenia diagnosed on routine laboratory tests. These abnormalities consisted of neutropaenia of 690/mm^3 (normal range 1700–7500/mm^3) and thrombocytopenia of 98,000/mm^3 (normal range 150,000–400,000/mm^3). Her past medical history was unremarkable. The bone marrow aspirate revealed mild hypoplasia, with dysplasia of both erythroid and granular lineages. Cytogenetic analysis revealed an isolated isochromosome 7q with no other clonal abnormality suggesting an underlying inherited bone marrow failure syndrome. A heterozygous mutation on both alleles of the Shwachman–Bodian–Diamond syndrome gene, located on the long arm of chromosome 7 at cytogenetic position 7q11, was identified and therefore confirmed the diagnosis of Shwachman–Diamond syndrome. Remarkably, the patient has remained completely asymptomatic so far with no history of repeated infections, steatorrhoea, dyspnoea, or palpitations.

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To explore other organ systems usually involved in this syndrome, further exams were performed. Radiographs of both femoral heads and knees were found to be normal and did not reveal any skeletal abnormality. The abdominal magnetic resonance imaging was consistent with pancreatic lipomatosis. Liver and pancreatic enzymes were normal. The electrocardiogram revealed a sinus rhythm with a left axis deviation. Transthoracic echocardiography revealed typical aspects of partial atrioventricular septal defect, with a 15 mm ostium primum atrial septal defect (Fig 1), a left-to-right shunt, and a mitral cleft (Fig 2) responsible for a mild-to-moderate mitral regurgitation. The left ventricular dimensions and both systolic and diastolic functions were normal. Moreover, no regional abnormality was observed. The right-sided cavities were enlarged, as a result of a significant interatrial shunt. No ventricular septal defect or any other associated abnormality was found. Interestingly, no familial history of congenital heart disease was reported. After discussion with the patient and her family, she was offered surgical cardiac repair and developed no complications after the surgical procedure. An echocardiographic assessment performed after surgery revealed good functional results with no residual septal defect. The patient is still regularly followed up by the haematology team and has shown no increase in cytopaenia.

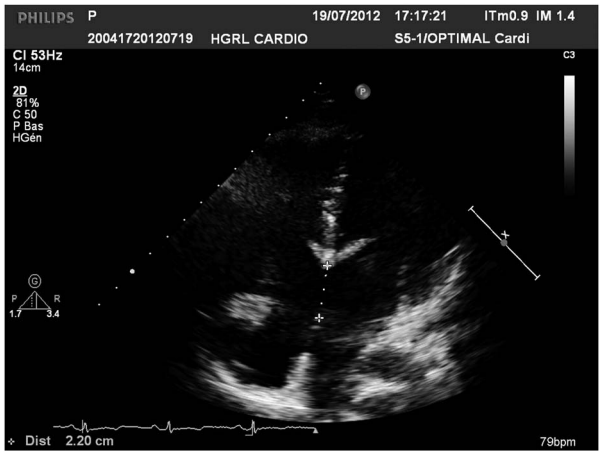

Figure 1.
Transthoracic echocardiography. Apical four-chamber view revealing the large ostium primum atrial septal defect measuring 22 mm.

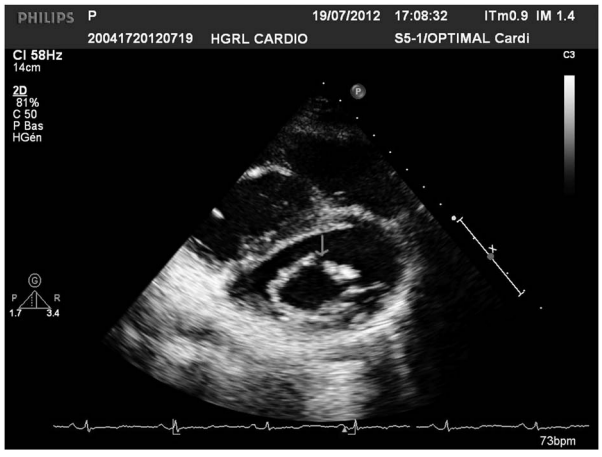

Figure 2.
Transthoracic echocardiography, parasternal short axis view revealing the mitral cleft. The white arrow indicates the location of the cleft of the anterior mitral leaflet.

Discussion

We report the first case of a young woman diagnosed with both the Shwachman–Diamond syndrome and partial atrioventricular septal defect.

In our patient, exploration of asymptomatic bicytopaenia led to diagnosis of the Shwachman–Diamond syndrome. Described first in 1964,[1] this multi-system disease is mainly characterised by haematological abnormalities but can also involve other systems, making the diagnosis challenging at times. It is an autosomal recessive disorder. Approximately 90% of patients with some of these clinical issues have various biallellic mutations in the Shwachman–Bodian–Diamond syndrome gene located on the long arm of chromosome 7.[2] These mutations lead to defects in a protein that participates in several essential cellular processes. Haematological abnormalities[3], including cytopaenia, are usually discovered early in life and are the most common findings revealing this syndrome. When considering haematological findings, neutropaenia occurs in more than 80% of cases, either chronic or intermittent, thrombocytopenia in 24–88%, and mild anaemia in up to 80% of patients. Pancytopaenia has been reported in up to 10–65% of cases. Neutropaenia, although not the only one, may contribute to the increased susceptibility to infections, emphasising the need for cautious prevention of potential systemic infections, particularly when prophylaxis of infective endocarditis is considered. The prognosis of these patients is impaired by the increased risk of developing myelodysplastic syndrome and secondary acute myeloid leukaemia, thus emphasising the need for a careful follow-up. Most patients have skeletal abnormalities,[3] including metaphyseal dysostosis, frequently involving femoral heads even if they remain usually asymptomatic at this level. The most commonly reported gastrointestinal impairment is exocrine pancreatic insufficiency of varying severity, due to extensive fatty replacement of pancreatic acinar tissue,[3] as documented in our patient, and may result in malabsorption, steatorrhoea, and failure to thrive in children. Cardiac abnormalities, although infrequently reported, have mostly been described through case reports[4–6] and include myocardial fibrosis and histopathological necrosis, possibly contributing to early deaths and cardiac failure. These features are of great interest when cardiotoxic chemotherapy is needed in case of stem cell transplantation.[7] Recently, a case of dilated cardiomyopathy with refractory cardiac failure was reported in a child with Shwachman–Diamond syndrome.[8] A large series of 102 patients with genetically demonstrated Shwachman–Diamond syndrome revealed that 11% of patients had cardiac abnormalities: six patients had cardiomyopathy and six had congenital heart disease. All congenital heart defects had been diagnosed within the first year of life and included two ostium secondum atrial septal defects, one ventricular septal defect, one double aortic arch, and one tetralogy of Fallot. Surgery was performed in four patients, whereas surveillance was chosen for the two remaining ones.[9]

Systematic cardiac evaluation in our patient revealed typical partial atrioventricular septal defect. The estimated incidence of atrioventricular septal defect ranges from 0.24/1000 live births to 0.31/1000 live births. This defect is usually associated with Down syndrome – trisomy 21 – but the responsible gene(s) on chromosome 21 have not been identified yet. When not associated with trisomy 21, atrioventricular septal defect usually

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occurs sporadically, with a multigenic pattern: some mutations in cysteine-rich with epidermal growth factor domains (CRELD) 1, located on chromosome 3, have recently been involved but are not sufficient to cause the defect when isolated.[10] Therefore, no genetic relation can so far be assumed between atrioventricular septal defect and Shwachman–Diamond syndrome.

In the absence of a familial history of congenital heart disease and Down syndrome, the partial atrioventricular septal defect diagnosed in our patient is likely to be the first described case in association with Shwachman–Diamond syndrome. The wide range of cardiac abnormalities diagnosed in such patients emphasises the need for a systematic cardiac screening of cardiac malformations and a regular monitoring of the cardiac function.

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Conflicts of Interest

None.

References

1. Shwachman H, Diamond LK, Oski FA, Khaw KT. The syndrome of pancreatic insufficiency and bone marrow dysfunction. J Pediatr 1964; 65: 645–663.
2. Costa E, Santos R. Hematologically important mutations: Shwachman–Diamond syndrome. Blood Cells Mol Dis 2008; 40: 183–184.
3. Dror Y, Donadieu J, Koglmeier J, et al. Draft consensus guidelines for diagnosis and treatment of Shwachman–Diamond syndrome. Ann N Y Acad Sci 2011; 1242: 40–55.
4. Savilahti E, Rapola J. Frequent myocardial lesions in Shwachman's syndrome. Eight fatal cases among 16 Finnish patients. Acta Paediatr Scand 1984; 73: 642–651.
5. Nivelon JL, Michiels R, Martres-Lassaunière MN, Passavy-Trouche AM, Petit A, Lorenzini JL. Myocardial fibrosis in Shwachman's syndrome: pathogenic discussion of cardiac complications. Pediatrie 1978; 33: 461–469.
6. Graham AR, Walson PD, Paplanus SH, Payne CM. Testicular fibrosis and cardiomegaly in Shwachman's syndrome. Arch Pathol Lab Med 1980; 104: 242–244.
7. Toiviainen-Salo S, Pitkänen O, Holmström M, et al. Myocardial function in patients with Shwachman–Diamond syndrome: aspects to consider before stem cell transplantation. Pediatr Blood Cancer 2008; 51: 461–467.
8. Kopel L, Gutierrez PS, Lage SG. Dilated cardiomyopathy in a case of Shwachman–Diamond syndrome. Cardiol Young 2011; 21: 588–590.
9. Hauet Q, Beaupain B, Michaud M, et al. Cardiomyopathies and congenital heart diseases in Shwachman–Diamond syndrome: a national survey. Int J Cardiol 2012 [Epub ahead of print].
10. Maslen CL. Molecular genetics of atrioventricular septal defects. Curr Opin Cardiol 2004; 19: 205–210.