Isolated thrombocytopenia in childhood: what if it is not immune thrombocytopenia?

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INTRODUCTION Childhood immune thrombocytopenia (ITP) remains a diagnosis of exclusion when isolated thrombocytopenia is not part of another disease process. In practice, the diagnosis of ITP can only be confirmed when thrombocytopenia resolves or is excluded after the recognition of a primary cause.

METHODS The records of 87 consecutive children with isolated thrombocytopenia seen over a nine-year period in a private paediatric haematology practice were reviewed retrospectively. Children in whom a primary cause was eventually found were the subjects of a further descriptive study.

RESULTS 9 (10%) children with isolated thrombocytopenia were not diagnosed with ITP because a primary disease was found. Of these nine cases, four had thrombocytopenia recognised during the neonatal period, consisting of perinatal cytomegalovirus infection (n = 2), meconium aspiration pneumonia (n = 1) and transient abnormal myelopoiesis associated with Down syndrome (n = 1). The remaining five children were each found to have familial thrombocytopenia, portal hypertension, cutaneous mastocytosis, May–Hegglin anomaly and systemic lupus erythematosus. Two of them had a history of failure of response to corticosteroid therapy.

CONCLUSION Secondary thrombocytopenia is not uncommon in a tertiary paediatric specialty practice with adequate evaluation. Thrombocytopenia occurring during the newborn period and failure of steroid therapy are predictive of secondary cases.

Keywords: differential diagnosis, idiopathic thrombocytopenic purpura, immune thrombocytopenia, neonatal thrombocytopenia, secondary thrombocytopenia
with thrombocytopenia during the first month of life. There were 32 patients from Singapore and 55 patients of other nationalities. 78 children were diagnosed with ITP. 41 (47.1%) of the 87 children had acute ITP with resolution of thrombocytopenia within three months of diagnosis, 9 (10.3%) had persistent ITP with disease resolution 3–12 months after diagnosis, and 14 (16.1%) had chronic ITP with thrombocytopenia lasting over 12 months. The other 14 (16.1%) children had otherwise typical clinical and laboratory features of ITP but did not have adequate follow-up information for classification.

Secondary thrombocytopenia was diagnosed in 9 (10.3%) children – 4 (80.0%) from the five neonatal onset cases and 5 (6.1%) among the 82 older children. According to nationality, secondary thrombocytopenia was diagnosed in 4 (12.5%) local patients and in 5 (9.1%) foreign patients. Their clinical features are summarised in Table I.

Two neonates were diagnosed with congenital/perinatal cytomegalovirus infection based on the presence of viral genome in the bloodstream. A newborn with Down syndrome was found to have hepatosplenomegaly and presence of megakaryoblasts on the blood film and was thus diagnosed with transient abnormal myelopoiesis. Another neonate was diagnosed with meconium aspiration pneumonia. Thrombocytopenia eventually resolved in these babies.

Among the older children with secondary thrombocytopenia, there were two familial cases. A seven-year-old child with mild thrombocytopenia had a strong family history indicative of an autosomal dominant form of familial thrombocytopenia. A two-year-old girl with mild thrombocytopenia failed to respond to prednisolone therapy prescribed by her primary physician and was found to have May–Hegglin anomaly on the blood smear. Family screening identified the same macrothrombocytopenia and presence of Döhle bodies in her asymptomatic father.

Secondary thrombocytopenia was also found in a two-year-old girl who had a history of recurrent urticarial and pigmented skin eruptions consistent with cutaneous mastocytosis. She had relapsing thrombocytopenia during infections with almost normal counts in between the episodes. A three-year-old presented with a history of persistent thrombocytopenia of six months’ duration and an isolated episode of anaemia following an episode of haematemesis. Prednisolone treatment was discontinued, as there was no response. He was well when he visited for a secondary opinion, and a small palpable spleen was the only positive sign on examination. Portal hypertension was suspected and was confirmed when oesophageal varices were found on upper endoscopy. The remaining patient was an eight-year-old girl who had frequent relapsing thrombocytopenia following successful treatment with prednisolone. A history of nonspecific facial rashes led to positive findings for antinuclear antibodies and anti-DNA antibodies.

**DISCUSSION**

In an unselected series of isolated thrombocytopenia in a specialist clinic, ITP remains the most frequent diagnosis in the great majority of cases after thorough evaluation. However, secondary thrombocytopenia is not uncommon and accounts for 10% of the cases in this series. Hence, clinicians following up with children who have isolated thrombocytopenia should be alert for alternative diagnoses other than ITP until the disease remits (Box 1).

The importance of enquiring for a familial history of bleeding or thrombocytopenic disorder cannot be overemphasised. A history of chronic ITP in a first-degree relative may be an important clue, as misdiagnosis of familial thrombocytopenia is common. Parental screening may be indicated at times. As clinical practice guidelines(2,3) and an abundance of case reports(4–9) have highlighted, when ordering additional tests and diagnostic procedures to look for other causes of thrombocytopenia, it is important to take note of atypical events from the patient’s history and abnormal signs other than bruises on physical examination. In this respect, neonatal onset thrombocytopenia represents a distinct clinical entity, and failure to respond to prednisolone therapy can be another warning sign of non-immune causes of isolated thrombocytopenia.

Examination of the peripheral blood smear is an important procedure in the evaluation of isolated thrombocytopenia.
The two cases of perinatal cytomegalovirus infection were identified because of atypical lymphocytosis found on the blood film (Fig. 1). This led directly to identification of the virus with DNA-based methods. In the case of Down syndrome, transient abnormal myelopoiesis was not initially suspected before the blood film examination, but the typical appearance of the blasts in the peripheral circulation helped to establish the diagnosis and preclude unnecessary treatment (Fig. 2).

The May-Hegglin anomaly belongs to a group of hereditary macrothrombocytopenia now known as myosin heavy chain 9 (MYH9)-related thrombocytopenia. Patients have giant platelets on the blood film and are often mistakenly diagnosed with ITP for this reason. However, careful attention to the leucocytes will reveal the typical cytoplasmic inclusions known as Döhle, or Döhle-like, bodies (Fig. 3). Correct diagnosis is important, as these patients are not responsive to corticosteroid or immune-based therapies. Some affected individuals are prone to developing auditory or renal diseases and proper family counselling and screening are often recommended.

The main limitation of this study was patient referral bias. As a private practice, it receives patients from a more affluent background, which may have restricted the full spectrum of thrombocytopenic illnesses. On the other hand, a mix of international patients may have introduced clinical entities associated with thrombocytopenia that have not been previously noted in the indigenous population. As alluded to earlier, it is unclear if the patients diagnosed with chronic ITP or those who are lost to follow-up truly have immune thrombocytopenia, because the disease does not have a specific laboratory marker.

In conclusion, secondary thrombocytopenia is not an uncommon diagnosis among children presenting with isolated thrombocytopenia and should be looked out for at the initial diagnosis and during the subsequent follow-up until thrombocytopenia resolves.
REFERENCES