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Case report 1

A boy with mild haemophilia A and eosinophilia-induced platelet dysfunction

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Key words: ecchymosis, mild haemophilia A, acquired platelet dysfunction with eosinophilia

Abstract

A 14-year-old boy presented with a recent onset of spontaneous ecchymosis and epistaxis. Investigations revealed moderate eosinophilia with normal platelet count, hypogranular platelets in peripheral blood smear, and prolonged bleeding time, suspected the possibility of acquired platelet dysfunction with eosinophilia (APDE). He was also found to have persistent marginally prolonged APTT, which created a diagnostic challenge. The bleeding symptoms, eosinophilia, bleeding time, and platelet hypogranularity resolved with a full course of anti-helminthic treatment supporting the diagnosis of APDE. Coagulation factor assay revealed marginally low factor VIII levels with normal von Willebrand antigen assay and activity; hence the diagnosis of asymptomatic mild haemophilia A was made.

Introduction

Acquired platelet dysfunction with eosinophilia (APDE) is a transient increase in bleeding tendency characterised by spontaneous bruising in the presence of marked eosinophilia. While spontaneous ecchymosis is the commonest bleeding manifestation, it can present with other uncommon presentations including epistaxis, gum or oral bleeding, gastrointestinal bleeding, haematuria, sub-conjunctival haemorrhage, and excessive bleeding after tooth extraction. This is a benign condition that usually doesn't require any specific therapy. The importance of recognising this condition is to avoid the pitfalls of diagnosing more serious bleeding disorders in children with ecchymosis. Meanwhile, haemophilia A is an inherited bleeding disorder due to mutated factor VIII gene which also leads to increased bleeding tendency with variable severity depending on the plasma factor VIII levels. Mild haemophilia A patients have factor levels between 0.05-0.40 IU/mL and are characterised by bleeding after trauma. Therefore they may not present until many years after birth and lack of awareness may lead to complicated clinical scenarios. Here I report a boy with asymptomatic mild haemophilia A presented with eosinophilia-induced acquired platelet dysfunction.

Case report

A 14-year-old boy was referred to the haematology unit with a history of on-and-off spontaneous ecchymosis over the trunk and limbs for one month and several episodes of nasal bleeding for one week duration. There was no past history or family history of bleeding. No recent upper respiratory infections or history of taking NSAIDs. On examination, multiple ecchymotic patches were seen on the trunk and limbs. The largest one was about 4 cm in diameter. There was no active nasal bleeding at the time of examination. Systemic examination was normal. His full blood count (FBC) showed Hb of 12.5 g/dL with normal red cell indices. Total white blood cell (WBC) count was 9.62×10^9/L, absolute eosinophil count was 2.28×10^9/L and platelet count was normal (233×10^9/L). His peripheral blood smear showed normochromic normocytic red cells and moderate eosinophilia. His platelets were adequate on the smear and showed some hypogranular forms (Figure 1).

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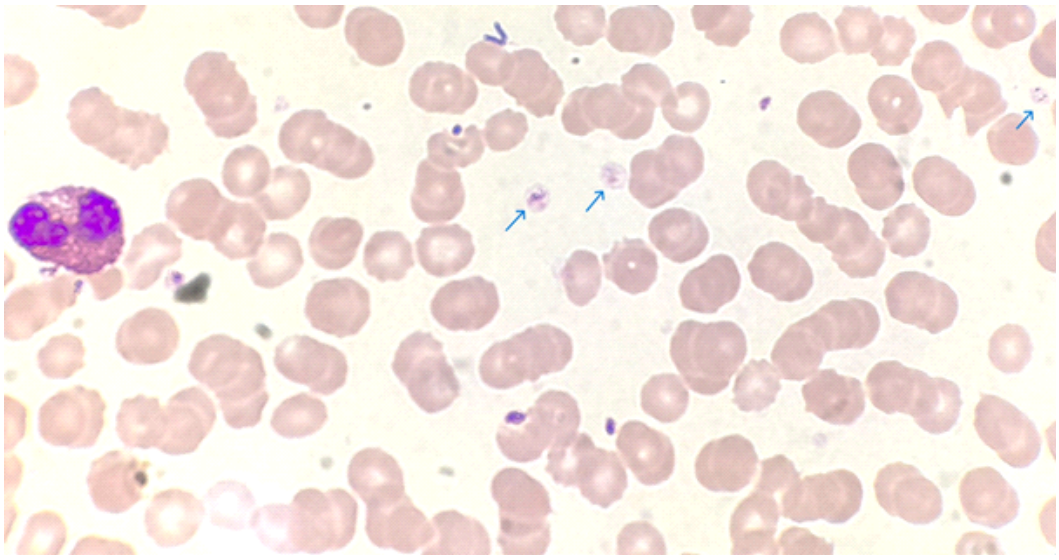

Figure 1. Peripheral blood smear, Leishman stain (40x), pale staining, empty-looking platelets with platelet hypo granularity (shown by arrow).

A prolonged bleeding time (BT) of 7 min was noted. His coagulation screening showed normal prothrombin time (PT) of 12.2 sec (10-14 sec) and persistent marginally prolonged activated partial thromboplastin time (APTT) of 39.5 sec and 38.9 sec (23-38 sec). Further, his non-EDTA smear showed only partial clumping of platelets. A platelet function test was planned. His liver and renal functions were normal and an ultrasound scan of his abdomen revealed no organomegaly. Parasitic screening performed includes stool for AOC (amoeba, ova, cysts), filarial antibodies IgM, IgG, toxoplasma antibodies IgM, IgG, and toxocara antibodies IgM which showed negative results. His toxocara IgG antibodies became weakly positive. He was started on empirical anti-worm treatment with mebendazole 100 mg twice daily for 3 days and diethylcarbamazine (DEC) 100 mg three times daily for 2 weeks. Local pathologies for nasal bleeding were excluded by performong an ENT referral. During the follow-up in the outpatient department, his eosinophilia was partially corrected (1.5 x10^9/L) and BT was lowered to 5 min. There was no further nasal bleeding but ecchymotic patches were still observed with reduced number and frequency. His APTT remained persistently prolonged. Mixing studies of APTT with normal plasma revealed 50% correction and inhibitor screening revealed no time-dependent inhibitors suspecting a coagulation factor deficiency. Because of persistent eosinophilia, he was given a trial of albendazole to cover possible toxocariasis as there was a history of having pet dogs and weakly positive toxocara IgG antibodies. He was referred to a reference center for coagulation factor assay and von Willebrand antigen assay. Investigations performed at the reference laboratory revealed normal BT and PT, normal thrombin time, and fibrinogen levels, with marginally prolonged APTT. Second-line investigations revealed normal von Willebrand factor antigen level and activity, normal ristocetin cofactor assay and normal factor IX levels. His factor VIII level was mildly low, 35.5% (50-150%) which was confirmed by repeating the test from a different laboratory (39.6%). Hence the diagnosis of mild haemophilia A was made. One month after the trial of albendazole his ecchymosis completely resolved. FBC showed normal eosinophil count (0.45x10^9/L), normal BT (2 min), and normal platelet morphology in blood picture (normal granularity of platelets) suggesting that APDE has resolved with anti-helminthic treatment. As the diagnosis of mild haemophilia A was an incidental finding, family screening was performed. One of his maternal uncles was also diagnosed as having mild haemophilia A and his only younger brother was found to have normal factor VIII levels.

Discussion

Acquired platelet dysfunction with eosinophilia (APDE) was first recognised in 1974 as a "non-thrombocytopenic purpura with eosinophilia"[1]. This condition is common in children from southeast Asia where parasitic diseases are endemic[2] and it is not an uncommon cause of non-thrombocytopenic purpura in Sri Lanka[3]. It is slightly more common in males with a male-to-female ratio of 1.15:1[4]. The usual presentation is widespread spontaneous bruising on the extremities and the trunk. Rarely severe bleeding can occur which may require platelet transfusions[4]. When considering etiology, the majority are secondary to parasitic infestations. The parasites most commonly identified with this syndrome are Ascaris, Enterobius, and Ancylostoma, Filaria and Toxacara[1]. This could also be secondary to eosinophilic inflammation such as asthma and hay fever. There are a few cases that etiology of eosinophilia is unknown but platelet function settles with anti-helminthic treatment[5]. Usually, the patients have a normal platelet count, but occasionally thrombocytopenia may be seen[6].

Abnormal platelet aggregation induced by collagen is the most common abnormality reported in these patients[4]. Abnormal ADP release from the platelets has been detected in these patients by the absence of a second wave of aggregation during stimulation of PRP by ADP or epinephrine. Abnormal or no ATP secretion from the platelets during stimulation by ADP, epinephrine, or collagen with normal ristocetin-induced platelet aggregation has also been noted[1,4]. (Figure 2) On peripheral blood film examination, abnormal platelet morphology was the most pathognomonic finding in 100% of cases. Hence, careful peripheral smear examination can enable timely diagnosis of APDE in patients with muco-cutaneous bleeding and eosinophilia[7].

Mild haemophilia is defined by factor levels between 0.05 and 0.40 IU/mL and is characterised by traumatic bleeds. A major issue associated with mild haemophilia A is that it may not present for many years after birth[8]. In a French cohort of 599 individuals born with haemophilia between 1980 and 1994, the median age at diagnosis of mild haemophilia was 28.6 months compared with 5.8 months for severe haemophilia and 9.0 months for the moderate form[9]. Accurate diagnosis of mild haemophilia A is also challenging. Sometimes APTT may not reveal underlying hemophilia A because of different sensitivities of reagents to FVIII levels[10]. Therefore, if there is a suspicion of haemophilia A, a factor assay should be performed, even if the APTT is normal. However, neither the one-stage nor the chromogenic assay always accurately reflects FVIII activity in individuals with mild haemophilia[11]. In the case of mild haemophilia A, in approximately 30% of patients, the level of measured FVIII varies according to which type of assay is used, leading to misdiagnosis or even lack of diagnosis[12]. Such assay discrepancies in haemophilia A occur in two ways [13]. Lower two-stage discrepancy (in which reduced factor levels are observed with the two-stage or chromogenic assay vs. the one-stage assay), and lower one-stage discrepancy (in which reduced factor levels are observed with the one-stage assay vs. the two-stage or chromogenic assay). Other challenges include large inter-laboratory variability between the findings of the tests, differences in factor levels due to physiological changes (examples include stress, acute phase reaction and blood group), overlap with the normal range of FVIII levels and increasing levels of FVIII in the elderly and during pregnancy[8]. There is no universal consensus as to whether the one-stage or chromogenic assay should be used to diagnose patients with mild haemophilia A, but in light of the discrepancies between the assays, the World Federation of Haemophilia (WFH) and others recommend that both assays are used[12]. In my patient, factor VIII level was confirmed by two different reference laboratories and both of them used one-stage assay for the detection of factor VIII level, as it is the widely available method in the government laboratories of Sri Lanka. Because of the challenges in accurate factor VIII level detection and delayed presentation, mild haemophilia is often underdiagnosed. Patients who are unaware that they have haemophilia may ignore symptoms until they become severe or complications have developed, leading to a more challenging clinical scenario.

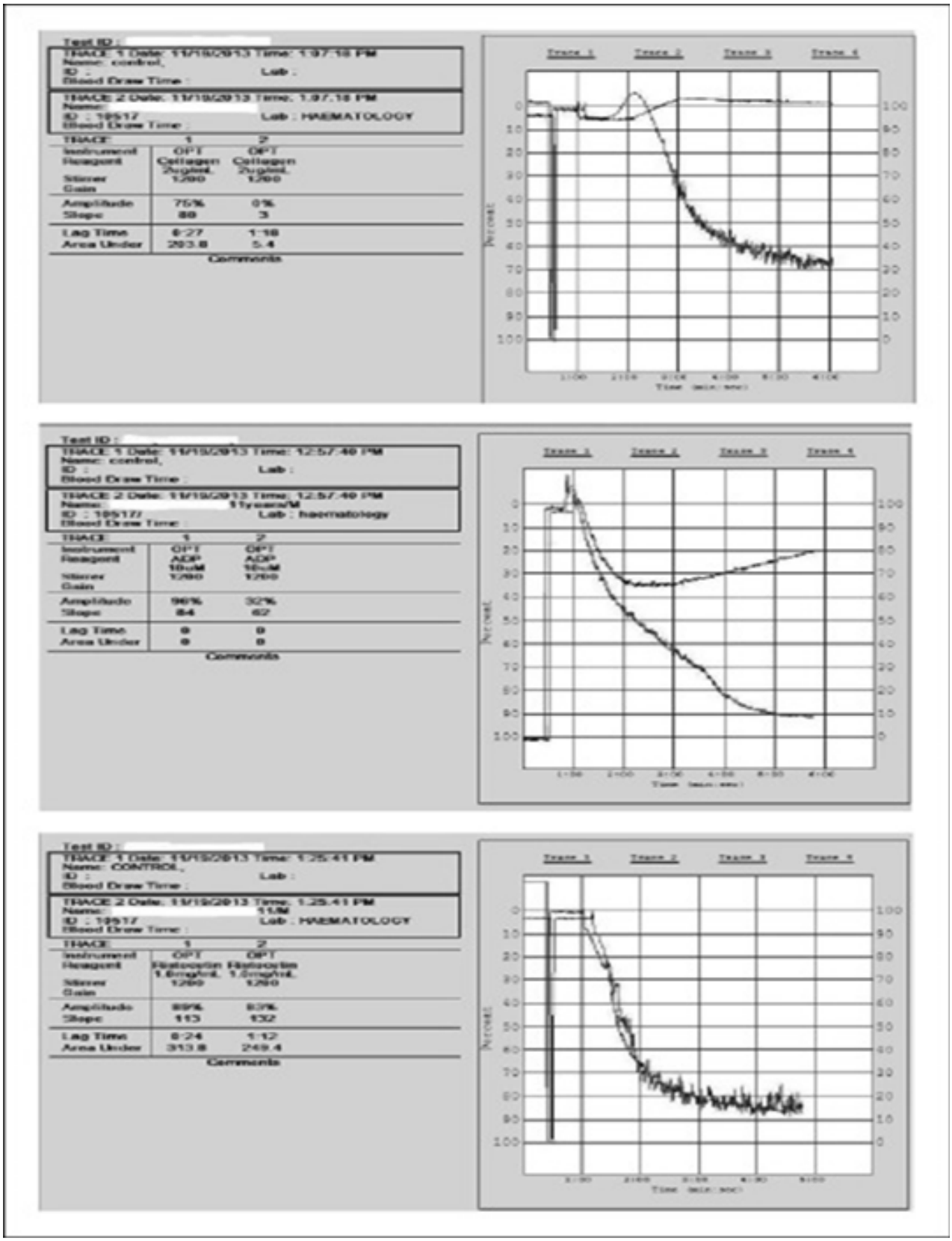

Figure 2. Platelet function test results in patients with APDE.

This case reports a 14-year-old child who presented with recent onset ecchymosis and nasal bleeding. His investigations revealed moderate eosinophilia with normal platelet count prolonged BT and hypogranular platelets in peripheral blood smear. The presence of an isolated marginally prolonged APTT with normal rest of the coagulation tests raised challenges in making the definitive diagnosis. Attention to the history, physical findings, simple laboratory tests, and examination of the platelet morphology on blood smears helps the diagnosis of APDE without going for more advanced and expensive investigations. Further in this case an incidental finding of marginally prolonged APTT facilitated the diagnosis of mild haemophilia A thereby early and correct intervention in future bleeding episodes and also identification of affected family members.

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