CASE REPORT

EDTA-induced pseudothrombocytopenia in association with bladder cancer

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SUMMARY

Pseudothrombocytopenia is the detection of low platelet counts by an autoanalyser despite lack of shortage in platelets. EDTA-induced pseudothrombocytopenia, the most frequently seen form in clinical practice, occurs mainly due to reaction of antiplatelet antibodies. Pseudothrombocytopenia is not only seen in healthy individuals but it is also reported in association with autoimmune, cardiovascular and liver parenchyma diseases and malignancy. We aimed to review approaches to pseudothrombocytopenia by presenting a case in which EDTA-dependent thrombocytopenia in association with bladder tumour was detected during examination for haematuria.

BACKGROUND

Thrombocytopenia, seen in approximately 2.5% of the general population, is defined as platelet count lower than $150\,000/\text{mm}^3$.¹ Pseudothrombocytopenia is the detection of low platelet counts by an autoanalyser despite lack of shortage in platelets. When a peripheral blood smear is evaluated, it is generally seen that platelet counts are within normal range in cases with pseudothrombocytopenia that is detected incidentally and not causing any bleeding diathesis. Currently, pseudothrombocytopenia phenomenon comprising a significant proportion of patients diagnosed as thrombocytopenia results from coagulation of blood sample in test tube, platelet satellitism, presence of giant platelets, platelet-induced autoagglutination and EDTA used as an anticoagulant in sample tubes.² EDTA-induced pseudothrombocytopenia, the most frequently seen form in clinical practice, occurs mainly due to reaction of antiplatelet antibodies including cold agglutinin type of IgG, IgM and IgA with platelet surface antigens.³

Pseudothrombocytopenia is not only seen in healthy individuals but also reported in association with autoimmune, cardiovascular and liver parenchyma diseases, malignancy, sepsis, viral infection and some medications.^{4–6} To the best of our knowledge, EDTA-induced pseudothrombocytopenia in association with bladder tumour has not been reported so far. We aimed to review approaches to pseudothrombocytopenia by presenting a case in which EDTA-dependent thrombocytopenia in association with bladder tumour was detected during examination for haematuria.

CASE PRESENTATION

An 80-year-old man presented to the urology outpatient clinic with symptoms of blood in urine for

over a month. He had undergone surgical resection and chemoradiotherapy with a diagnosis of colon adenocarcinoma 9 years ago; while in remission the patient had been followed without drug therapy for 8 years. Complete blood count (CBC) revealed a platelet count of $15 \times 10^3/\text{mm}^3$; thus the patient was referred to the internal medicine department. *Six months prior platelet count was normal.* There was no abnormal finding in the physical, including urogenital, examination. *The patient did not define any viral or bacterial infection.* Similarly, biochemical tests were considered normal. In the urinalysis there was an excessive number of red blood cells and leucocytes, but no growth in the urine culture test. Peripheral blood smear was performed; the patient had gross haematuria and thrombocytopenia but there were no findings suggesting bleeding diathesis such as petechiae, purpura and ecchymosis in the physical examination. Platelet count was detected as $141 \times 10^3/\text{mm}^3$ when CBC was re-evaluated by using citrate tubes instead of EDTA tubes in the patient who had clustered platelets on the peripheral blood smear (*figure 1*).

The patient was diagnosed with EDTA-induced pseudothrombocytopenia, given lack of clinical signs of bleeding diathesis despite decreased platelet counts and sufficient number of platelets on peripheral blood smear and in CBC with citrate tubes. Pelvic sonography was performed to reveal the cause of haematuria, as pseudothrombocytopenia was found not to be linked to a bleeding diathesis. On sonography there were diffuse irregularities and thickness on the bladder wall; cystoscopy was performed, which revealed wide-based papillary lesions (1–1.5 cm in width) in four areas at right wall and roof of the bladder. Transurethral resection (TUR) was performed to available lesions. No complication was observed during and after TUR-bladder tumour. The patient was referred to the medical oncology department as histopathological evaluation was reported as a low-grade transitional cell bladder tumour (*figure 2*).

DISCUSSION

Pseudothrombocytopenia is a phenomenon, without any dysfunction in the number or function of platelets, which can be readily missed if not considered in the differential diagnosis. This phenomenon can cause unnecessary surgical interventions and platelet transfusions if not kept in mind.^{7–8} In some cases it may cause failure or delay in receiving required therapies, especially surgical interventions, as patients are considered thrombocytopenic. In the literature there are patients with

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Figure 1 The peripheral smear of the EDTA-anticoagulated blood showing platelet clustering (arrows).

pseudothrombocytopenia who failed to undergo reperfusion therapy since they were considered profoundly thrombocytopenic during acute myocardial infarction, or who underwent splenectomy with the diagnosis of immune thrombocytopenic purpura.⁹

EDTA-induced pseudothrombocytopenia is detected in 0.1% of patients referring to hospitals that serve routine healthcare, while the rate increases to 15% in facilities evaluating thrombocytopenia aetiology.⁹ Pseudothrombocytopenia incidence is

rather low with other anticoagulants such as heparin and sodium citrate.

The mechanism by which EDTA causes thrombocytopenia is unclear. Lack of EDTA-induced thrombocytopenia in Glanzmann disease (glycoprotein (Gp) IIb/IIIa deficiency) leads to a hypothesis suggesting that antibodies activated in the presence of EDTA may cause in vitro platelet aggregation by binding to Gp IIb/IIIa receptors on the platelet surface.³ Calcium is required for maintaining the heterodimeric structure in Gp IIb/IIIa. It is thought that activation of EDTA-related calcium cascade causes interaction between Ca and platelet antibodies by removing Ca from Gp IIb or Gp IIIa binding sites.

Although no precise information exists regarding formation of antiplatelet antibodies, it is proposed that fragmented platelets may present cryptic antigens that trigger synthesis of antiplatelet antibodies. In these patients it was shown that platelet-related antibodies develop against Gp Ia/IIa, Gp Ib/IX or Gp IIb/IIIa.¹⁰ In addition, it is also thought that antibodies developing against infectious agents and several drugs may trigger platelet aggregation through cross reaction with platelets.¹¹ In a study by Bizzaro *et al*¹² it was failed to demonstrate an apparent association between antiplatelet antibodies and thymic neoplasm in patients with thymoma. In that study it was reported that platelet aggregation was observed a few years after diagnosis of thymoma; moreover, the phenomenon persisted after surgical resection of tumour. In another study on patients with cancer with EDTA-induced thrombocytopenia, no association was found between malignancy type and pseudothrombocytopenia.¹³ Pseudothrombocytopenia is not only seen in healthy individuals but also reported in relation with autoimmune, cardiovascular and liver parenchyma diseases, malignancy, sepsis, viral infection and some medications. It is also reported in patients with malignancies such as breast cancer, multiple myeloma, neuroendocrine carcinoma and thymoma. However, this is the first case report presenting association of bladder tumour and EDTA-related thrombocytopenia.

Figure 2 Pathological examination of the mass revealing transitional cell bladder carcinoma.

Learning points

- ▶ As in our case, presentation with a bleeding symptom can make it difficult to consider pseudothrombocytopenia for diagnosis.
- ▶ All decreased platelet counts detected by autoanalysers should be confirmed by peripheral blood smear.
- ▶ In case of suspicion, blood anticoagulated with EDTA should be immediately studied using preheated tubes and results confirmed using different anticoagulants such as citrate, sodium oxalate or heparin.

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Competing interests None.

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