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Ethylenediaminetetraacetic acid-dependent pseudothrombocytopenia associated with neuroendocrine carcinoma: A case report

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Abstract. Ethylenediaminetetraacetic acid-dependent pseudothrombocytopenia (EDTA-PTCP) is an *in vitro* phenomenon of EDTA-induced platelet aggregation at room temperature. This phenomenon consists of platelet clumping due to anti-platelet antibodies in blood anticoagulated with EDTA. It has been reported in patients with various diseases, including sepsis, multiple myeloma, acute myocardial infarction and breast cancer. Since unrecognized EDTA-PTCP may lead to inappropriate treatment, it should always be considered as a possible cause in patients with low platelet counts. This study identified a case of transient EDTA-PTCP in a patient with neuroendocrine carcinoma of the stomach. In the present study, a 50-year-old male presented with epigastric pain and a weight loss of 15 kg. The patient presented with EDTA-PTCP and was diagnosed with neuroendocrine carcinoma of the stomach. Following systemic chemotherapy, the tumor showed a marked regression and the EDTA-PTCP disappeared. The mechanism by which this occurred is not clear but an association of EDTA-PTCP with neuroendocrine carcinoma is strongly suggested.

Introduction

Ethylenediaminetetraacetic acid (EDTA) is commonly used as an anticoagulant in sampling tubes for blood cell counts. EDTA-dependent pseudothrombocytopenia (EDTA-PTCP) is an *in vitro* phenomenon consisting of EDTA-induced platelet aggregation at room temperature (1). This phenomenon occurs due to anti-platelet antibodies that cause platelet clumping in blood that had been anticoagulated with EDTA. EDTA-PTCP may be recognized by the presence of platelet clumps in the peripheral blood smear.

EDTA-PTCP has been observed in a general hospital, with a prevalence of 0.1% (2,3). It has been reported in patients with various diseases, including sepsis, multiple myeloma, acute myocardial infarction and breast cancer (4-7). Since unrecognized EDTA-PTCP may result in inappropriate treatment, it should always be considered as a possible cause of low platelet counts in patients.

This study reports a case of transient EDTA-PTCP observed in a patient with neuroendocrine carcinoma of the stomach. The case report was approved by the Institutional Review Board (IRB). As it involved no risk to the patient, the waiver of informed consent was allowed by the IRB.

Case report

A 50-year-old male presented with epigastric pain lasting for one month and a weight loss of 15 kg. Physical examination revealed epigastric tenderness. The patient had no history of bleeding problems and there was no family history of hemorrhagic disorders. The patient did not use alcohol or any medication.

An initial complete blood count (CBC) using EDTA as an anticoagulant revealed a low platelet count ($19x10^3$ platelets/μl). The biochemical tests were within the normal ranges. The microscopic examination of the peripheral blood smear revealed platelet clumping (Fig. 1). CBC using sodium citrate as anticoagulant revealed a normal platelet count ($236x10^3$ platelets/μl).

Gastroduodenoscopy revealed a large ulcerated mass from the cardia to the fundus of the stomach (Fig. 2). Endoscopic biopsies of the mass confirmed the diagnosis of small cell neuroendocrine carcinoma (Fig. 3). Computed tomography (CT) scans of the abdomen revealed an irregular mass with perigastric infiltration in the stomach and a metastatic mass in the liver (Fig. 4).

Systemic chemotherapy using etoposide and cisplatin was performed. Following four cycles of chemotherapy, the

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Key words: pseudothrombocytopenia, ethylenediaminetetraacetic acid, neuroendocrine carcinoma

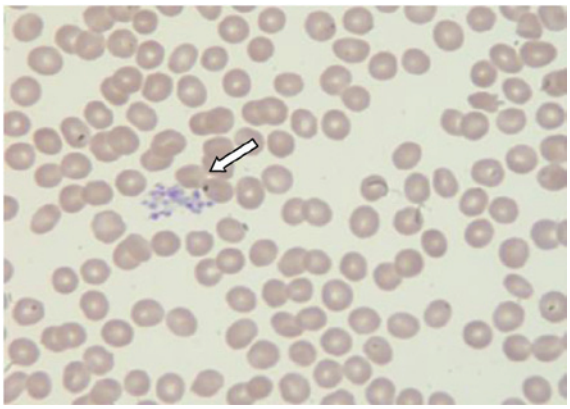

Figure 1. The peripheral smear of the EDTA-anticoagulated blood showed platelet clumping (arrow). EDTA, ethylenediaminetetraacetic acid.

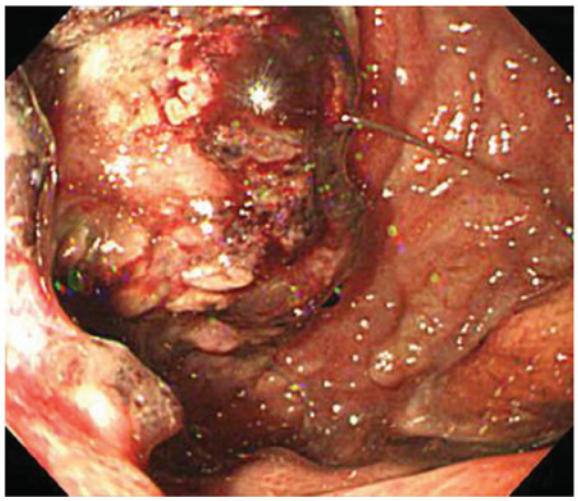

Figure 2. Gastroduodenoscopy revealed a large ulcerated mass in the stomach.

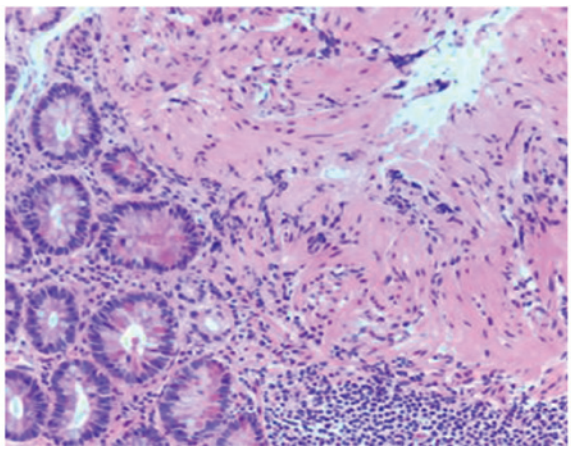

Figure 3. Pathological examination of the mass revealed small cell neuroendocrine carcinoma (hematoxylin and eosin stain; magnification, x200).

follow-up CT scan showed marked tumor regression (Fig. 5). Platelet clumping on the peripheral blood smear disappeared and the platelet count in blood anticoagulated with EDTA was also normalized.

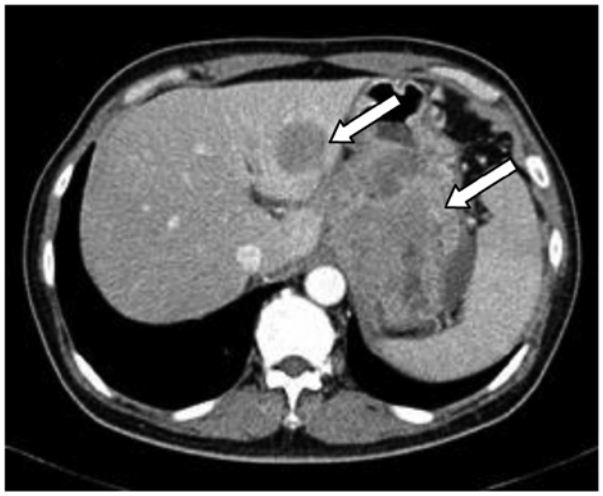

Figure 4. The initial CT scans of the abdomen revealed an irregular mass with perigastric infiltration in the stomach and a metastatic mass in the liver (arrows). CT, computed tomography.

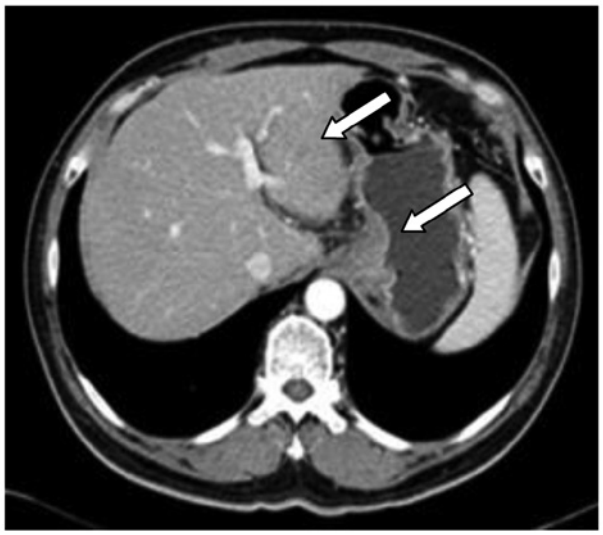

Figure 5. The follow-up CT scans after four cycles of chemotherapy revealed marked tumor regression. CT, computed tomography.

Discussion

PTCP is of practical significance in consequent clinical decisions or therapeutic interventions (6). In the evaluation of patients with thrombocytopenia, a key first stage is to rule out PTCP, particularly in patients without an apparent cause for thrombocytopenia. PTCP is an *in vitro* artifact that results in erroneous platelet counts. PTCP is caused by *in vitro* platelet clumping which is induced by antibody-mediated agglutination secondary to platelet activation resulting from inadequate blood sampling or delayed introduction to an anticoagulant in the test tube.

EDTA is commonly used as an anticoagulant for CBC. EDTA-PTCP occurs due to anti-platelet autoantibodies that cause platelet clumping in the presence of EDTA (4,8). These antibodies, usually IgG but also IgM and IgA, recognize platelet antigens on the platelet membrane modified by

EDTA (1,9), which results in platelet agglutination. Automatic analyzers interpret platelet clumps as white blood cells (3). If thrombocytopenia is obtained in EDTA-anticoagulated blood, microscopic evaluation of the peripheral blood smear should be performed. In addition, the platelet count should be determined in blood collected into sodium citrate or heparin. In this case, the peripheral blood smear showed platelet clumps and the platelet count was normalized in blood that was anticoagulated by sodium citrate.

EDTA-PTCP has been identified in healthy subjects and patients with various conditions, including gastrectomy, autoimmune diseases, liver diseases, cardiovascular diseases and viral infections (4,5,10-14). EDTA-PTCP has also been reported in association with neoplastic diseases, including breast cancer and multiple myeloma (6,7). It has been suggested that damaged platelets in a variety of diseases may expose cryptic antigens and induce the synthesis of anti-platelet antibodies (4,15). Platelet-associated autoantibodies against glycoprotein (GP) Ia/IIa, Ib/IX or IIB/IIIA have been detected in these patients (4,7). However, the clinical relevance of EDTA-dependent anti-platelet autoantibodies remains uncertain.

To the best of our knowledge, this is the first case of EDTA-PTCP occurring in a patient with neuroendocrine carcinoma. In the current patient, EDTA-PTCP coincided with neuroendocrine carcinoma and disappeared following chemotherapy with marked tumor regression. The mechanism by which this occurred is not clear but an association of EDTA-PTCP with neuroendocrine carcinoma is suggested.

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