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Case Report

Microangiopathic Hemolysis Refractory to Plasmapheresis Responding to Docetaxel and Cisplatin

A Case Report

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Abstract

We report the case of a 56-yr-old woman with adenocarcinoma of unknown origin metastatic to the bone marrow presenting with a thrombotic thrombocytopenic purpura-like syndrome refractory to protracted daily plasmapheresis and steroids but readily and completely responsive to docetaxel plus cisplatin. Sustained and complete response was pathologically confirmed.

Key Words: Adenocarcinoma of unknown origin; thrombotic thrombocytopenic purpura; taxanes; cisplatin; plasma exchange; protein-A immunoadsorption; alkylating agents.

Introduction

Adenocarcinoma of unknown origin metastatic to the bone marrow is uniformly fatal with a reported median survival of 1 mo *(1)*. Review of the pertinent literature includes a case report with microangiopathic hemolysis relatively refractory to plasmapheresis that responded to chemotherapy but had a short survival of 3 mo *(2)*. Previous publications have shown that plasmapheresis probably has a limited or no therapeutic role in this rare and fatal malignant complication *(3,4)*. The present case report describes (1) the role of further investigation, including a bone marrow examination in patients presenting with a thrombotic thrombocytopenic purpura (TTP)-like syndrome with no other clinical or imaging evidence of malignancy, and (2) the prompt resolution of the hemolytic syndrome in response to successful chemotherapy.

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Case Report

A 56-yr-old woman with adenocarcinoma of unknown origin (AUO) presented with complaints of malaise, fatigue, jaundice, dark urine, and pallor of 1-wk duration. There were no palpable lymphadenopathy or hepatosplenomegaly or central nervous system manifestations, although a mild proteinuria with a normal creatinine level had been noted. A laboratory investigation showed anemia (Hb, 6.2 g/dL), marked thrombocytopenia (platelets, 62×10^9/L), indirect hyperbilirubinemia (total, 2.4 mg/dL; direct, 0.3 mg/dL), marked elevation of lactate dehydrogenase (LDH) (4983 U/L), reticulocytosis (14.9%, corrected), and schistocytosis on peripheral blood smear.

The serum alkaline phosphatase was 299 U/L. All other studies, including a coagulation profile and serum metalloprotease, were normal *(5)*. A clinical diagnosis of a TTP-like syndrome was made and the patient was immediately started on plasmapheresis. Over a course of 27 d, the patient had received 20 plasma-exchange sessions, 5 filtrations through a protein-A immunoadsorption column (Prosorba®), 4 doses of vincristine (1.0 mg per dose, IVP on d 1, 4, 7, and 10) *(6)*, 3 consecutive daily doses of intravenous human globulin (30 g per dose), and daily high-dose steroid (250 mg methylprednisolone iv every 8 h). A total of 402 units of blood components (35 units of packed red blood cells, 365 units of plasma, and 2 units of monodonor platelets) were administered.

Despite this aggressive intervention, massive hemolysis continued and worsened even during plasmapheresis. On plasmapheresis d 27, there were persistent abnormalities, including a Hb of 7.4 g/dL, total bilirubin of 1.1 mg/dL, LDH of 1824 U/L, and a reticulocyte count of 11.3%. Bilateral bone marrow biopsies were obtained and revealed an infiltrative malignant pattern with fibrosis and necrosis, suggesting adenocarcinoma metastatic to the bone marrow (Fig. 1A). Immunostaining revealed the tumor cells to be CAM 5.2 and CK 7-positive (keratin antigen) but negative for estrogen and progesterone receptors, thyroid transcription factor, gross cystic disease fluid protein-15 (BRST-2), and lymphoid markers. Bone-derived alkaline phosphatase was elevated at 625 U/L. A computed tomography of the head, chest, abdomen, and pelvis along with a broad spectrum of tumor markers, including β-HCG and α-fetoprotein were all noncontributory. A breast sonogram and mammography were also negative. A clinical diagnosis by exclusion of AUO metastatic to the bone marrow was made and the patient was started on combination treatment with cisplatin and docetaxel, 75 and 85 mg/m^2, respectively. Proper hydration prior to cisplatin with 2 L of half-normal saline given iv over 2 h, including potassium supplementation as needed and premedication prior to docetaxel with diphenhydramine (50 mg iv), acetaminophen 650 mg, and dexamethasone 10 mg po bid for 3 consecutive days starting on the day prior to chemotherapy were routinely administered.

There was an immediate hematologic recovery, including a disappearance of schistocytosis and normalization of the bilirubin and LDH levels shortly after the administration of the first cycle of chemotherapy; on postchemotherapy d 8, there was a rise of Hb to 11.2 g/dL and of platelets to 234× 10^9/L associated with a decrease of the LDH to 1321 U/L, serum bilirubin to 0.2 mg/dL, and the reticulocyte count to 3.3%, and the patient was rendered transfusion independent at that time.

Serial bone marrow biopsies taken following the fourth and sixth cycle of chemotherapy (Fig. 1B) showed a significant pathologic response with minimal residual disease present after the sixth cycle. Currently, the patient continues improving after 12 cycles of treatment, as demonstrated by a bone marrow trephine comprising healthy marrow tissue only (Fig. 1C) shortly after the completion of the eighth cycle of chemotherapy.

Discussion

The initial presentation of this case report indicated active microangiopathic hemolysis, which could be the result of a TTP-like syndrome. Multiple plasmaphresis sessions, high-dose steroids, vincristine, and protein-A immunoadsorption did not improve the active hemolytic process but did help in the stabilization of the patient's hematologic and renal functions until a diagnosis could be established and a proper effective treatment could be initiated. Conversely, it is possible that the ongoing massive hemolysis might have adversely affected the patient's renal function if it were not for the supportive daily plasmapheresis and transfusions. The continuous removal of hemolyzed plasma may provide a beneficial supportive role in the management of patients with TTP-like microangiopathic hemolysis and thrombocytopenia where a definitive diagnosis has not been reached. Cases of plasmapheresis and steroid–refractory–TTP presenting with massive microangiopathic hemolysis and thrombocytopenia may need to be rigorously investigated to rule out occult underlying malignancy including a bone marrow examination as shown in the present case.

The addition of taxanes to platinum *(7)* analogs is an interesting therapeutic option in the manage-

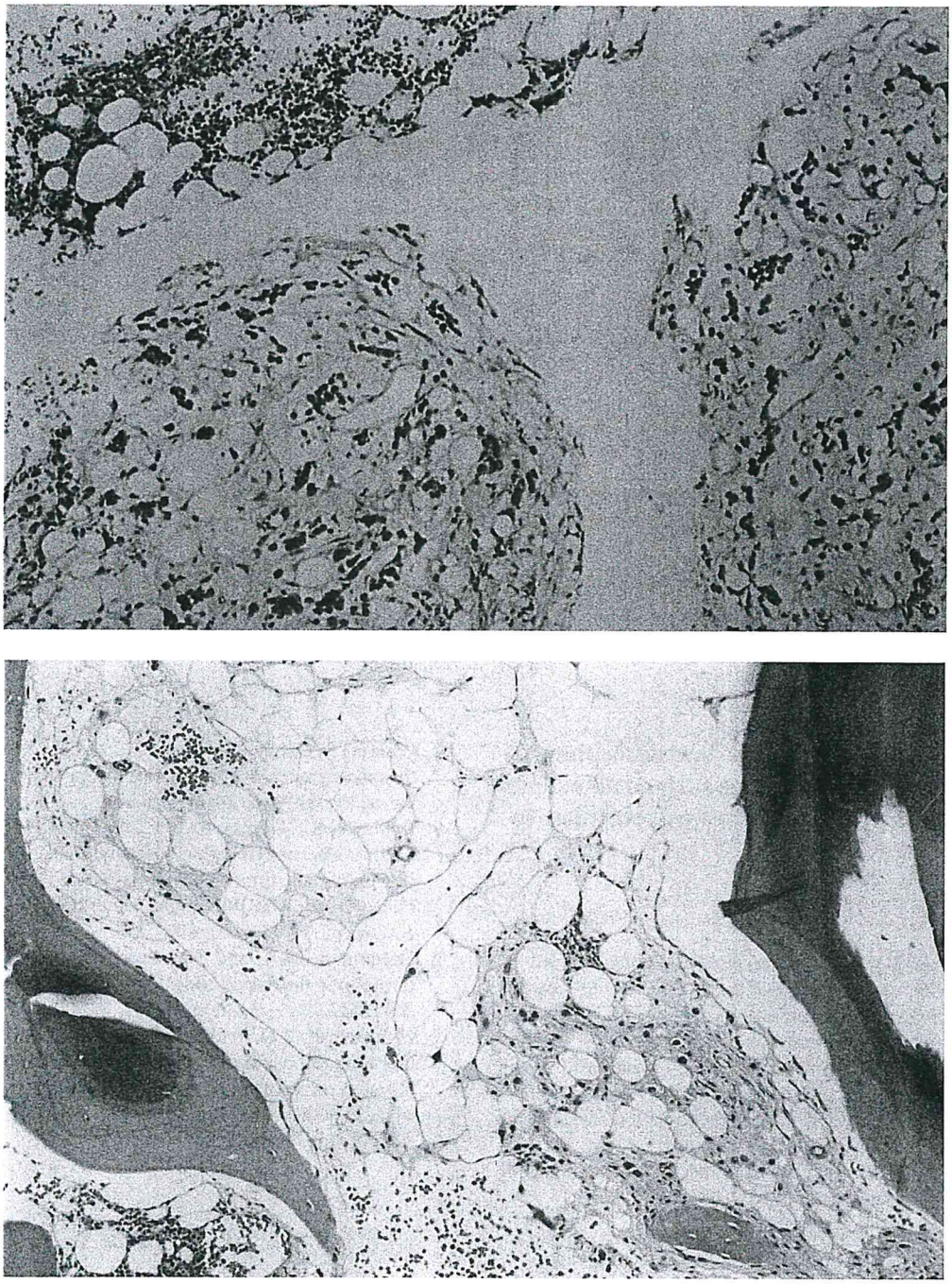

Fig. 1. Bone marrow trephines taken just prior to the initiation of chemotherapy **(A)** H&E, 200×) and shortly after the administration of the fourth **(B)** (H&E, 100×) and the eight **(C)** (H&E, 100×) cycles of chemotherapy with docetaxel and cisplatin. Note the presence of scanty hematopoietic cells at the bottom of **(A)** and the gradual replacement of the malignant infiltrates by the normal hematopoietic precursors in **(B)** and **(C),** culminating in the complete response shown in **(C).** (*continues*)

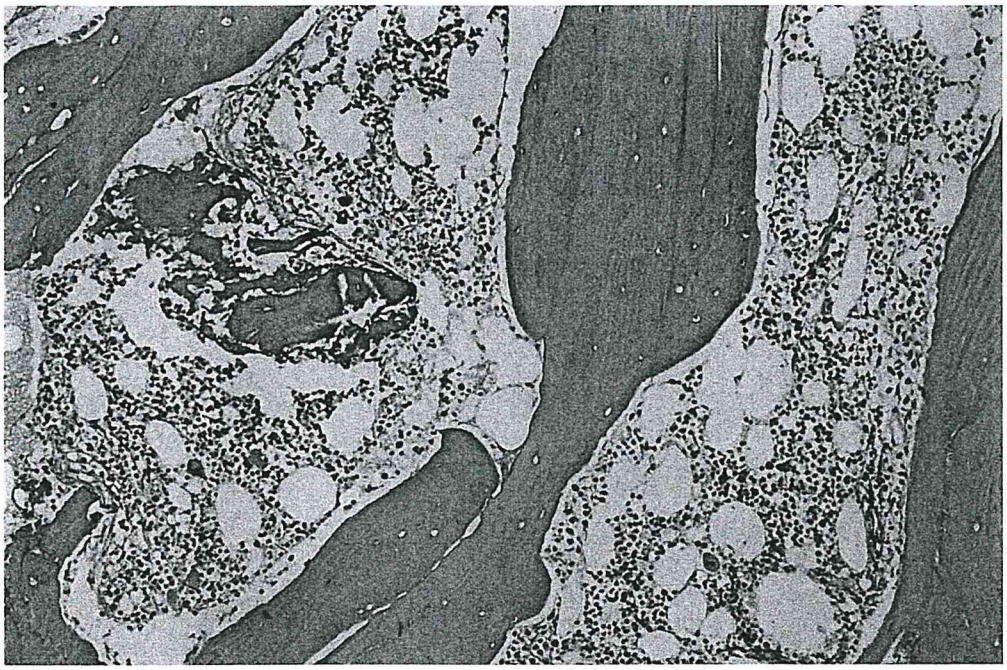

Fig. 1. (*continued*)

ment of AUO and we plan to initiate a phase II study to evaluate the efficacy of such combinations in the management of AUO with or without microangiopathic changes.

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