Pancytopenia Associated with a Granulosa-cell Tumor of the Ovary

Report of a Case

VICTOR M. NAPOLI, M.D., AND HOWARD WALLACH, M.D.

Department of Pathology and Laboratory Medicine and Department of Medicine, Emory University School of Medicine, Atlanta, Georgia 30322

ABSTRACT

Napoli, Victor M., and Wallach, Howard: Pancytopenia associated with a granulosa-cell tumor of the ovary. Report of a case. Am J Clin Pathol 65: 344-350, 1976. An unusual case of pancytopenia associated with a granulosa-cell tumor of the ovary in a 44-year-old woman is reported. Initially the patient was thought to have the rare, but well recognized, syndrome of hemolytic anemia complicating an ovarian tumor. However, laboratory studies and clinical follow-up ruled out hyperhemolysis and documented a condition of bone-marrow failure. Excision of the massive tumor was followed by hematologic recovery, which has now lasted more than a year and a half. (Key words: Pancytopenia; Bone-marrow failure; Granulosa-cell tumor; Ovary.)

A HEMOLYTIC ANEMIA of probable immune pathogenesis occurs as a complication in some patients with ovarian tumors.4,6-8,20 The published cases of this syndrome, now totaling 25, were reviewed by Bernstein and associates.3 The anemia is usually severe, with high reticulocytosis and a positive Coombs test. Seldom, a mild thrombocytopenia is present.8,14,16 Steroids, cytotoxic drugs, and splenectomy are ineffective, and only surgical excision of the tumor brings about hematologic recovery. Almost always the tumor is a dermoid cyst, a teratoma, or an adenocarcinoma, but recently Dawson and associates described the first case of granulosa-cell tumor with hemolytic anemia.7 Since the neoplasm was necrotic, the microscopic diagnosis was arrived at on the basis of the reticulin pattern.

We have studied a patient who had severe pancytopenia and a large well-preserved ovarian neoplasm conclusively identified as a granulosa-cell tumor. We are presenting this case because it confirms the report of Dawson and associates of hematologic complications occurring in association with this type of neoplasm.7 At the same time, ours differs from all previously published cases, since there was no hyperhemolysis in our patient.

Report of a Case

First Hospitalization. A 44-year-old postmenopausal Negro woman was admitted to Grady Memorial Hospital November 3, 1972, because of severe dyspnea and abdominal swelling. She was cachectic and in
cardiac failure. A firm mass, 30 x 15 cm., the size of a 16-week pregnancy, was palpated in the lower abdomen. Hematocrit was 6%, leukocyte count was 5,900 per cu. mm., and platelets were 39,000 per cu. mm. Examination of the peripheral blood smear revealed anisocytosis, poikilocytosis, hypochromia, and one nucleated erythrocyte per 100 leukocytes. The differential was: 39% segmented neutrophils, 3% bands, 3% metamyelocytes, 54% lymphocytes, and 1% monocytes. The reticulocyte count, corrected for the low hematocrit, was 0.45%, indicating no response to the profound anemia. Direct and indirect Coombs tests were negative. Serum iron was 260 μg. per 100 ml., with a total iron-binding capacity of 282 μg. per 100 ml. and 92% saturation. Serum haptoglobin was 217 mg. per 100 ml. (normal: 50–150). SGOT was 1040 mU., and LDH was 8700 mU., with a heat-stable fraction of 376 mU., showing that most of the increase was in the heat-labile hepatic fraction. pH was 7.0, P02 153 mm. Hg, and PC02 13 mm. Hg. The severe acidosis was ascribed to anemia and cardiac failure. Following infusion of 4 units of packed erythrocytes the hematocrit increased to 30%. Attempts at bone marrow aspiration were unsuccessful. During the hospital stay the patient had a brief septicemic episode, which promptly yielded to gentamicin. Blood cultures grew Herellea vaginicola. The patient refused surgery for the pelvic mass, and left the hospital November 15, 1972.

**Second Hospitalization.** The patient was readmitted May 6, 1973. Again, she was dyspneic and in cardiac failure. The pelvic mass had increased to the size of a 22-week pregnancy. Hematocrit was 7%, leukocyte count 4,900 per cu. mm., and platelets were 60,000 per cu. mm. After infusion of three units of packed erythrocytes the hematocrit increased to 30%. Serum haptoglobin was 130 mg. per 100 ml. (normal: 50–150); serum iron was 104 μg. per 100 ml., with a total iron-binding capacity of 186 μg. A bone-marrow aspiration was unsuccessful, but an iliac-crest needle biopsy revealed hypocellular bone marrow with traces of iron (Fig. 1). For two weeks, folic acid, 1 mg. daily, and ferrous sulfate, 540 mg. daily, were administered, with no reticulocyte response. On May 21, the patient underwent hysterectomy and bilateral salpingo-oophorectomy with removal of a large right ovarian tumor. Before and after operation, 18 units of platelet concentrate were administered to prevent bleeding from thrombocytopenia. On gross examination the tumor was found to replace completely the right ovary. It measured 20 x 10 x 8 cm., weighed 1,550 Gm., and was white-gray and smooth on the external surface, except in a few focal areas where it was covered by fibrous adhesions. On sectioning the neoplasm was gray-brown and soft, and contained several irregular cystic spaces of various sizes. A few cysts contained bloody fluid, and others were filled with clear fluid (Fig. 2). Also submitted for pathologic examination were both fallopian tubes and the contralateral ovary, which were found to be grossly unremarkable. The uterus weighed 80 Gm. and showed no abnormality on the external surface. The endometrial cavity was small. Microscopic examination disclosed that the neoplasm was composed of polygonal granulosa cells with scanty cytoplasm and indistinct cellular borders, forming diffuse sheets, or arranged in a cylindromatous pattern (Fig. 3). Only a few foci of luteinization were seen, and mitoses were rare. Large deposits of hemosiderin, the obvious sequel of local bleeding, were present. Microscopic sections of the uterus revealed a proliferative endometrium with rare cystic glands. The postoperative course was uneventful. At the time of discharge, on May 28, hematocrit was 32%, leukocyte count 2,900 per cu. mm., and platelets were still low. The peripheral blood counts progressively increased in the next two
FIG. 1. Bone marrow before operation, showing hypocellularity and decrease in myeloid precursors. Hematoxylin and eosin. ×500.

FIG. 2. Bisected granulosa-cell tumor of the ovary. There are cystic and hemorrhagic areas.
months (Fig. 4), but afterwards the patient failed to return to the clinic and was temporarily lost to follow-up.

**Third Hospitalization.** The patient was readmitted March 7, 1974 because of hypertension. Hematocrit was 37%, leukocyte count 6,800 per cu. mm., and platelets were 480,000 per cu. mm. The differential was: 73% segmented neutrophils, 1% bands, 20% lymphocytes, 3% monocytes, and 3% eosinophils. The corrected reticulocyte count was 3.7%. Bone-marrow smear and biopsy confirmed the hematologic recovery, showing increased cellularity and adequate megakaryocytes (Fig. 5). Results of sugar-water test, hemoglobin electrophoresis, and a screening test for G-6PD deficiency were normal.

**Discussion**

In our case the laboratory studies ruled out the initial diagnosis of hemolytic anemia with an ovarian tumor, made at the time of the patient's first admission. The reticulocyte counts indicated a lack of marrow response, the direct and indirect Coombs tests were negative, and serum haptoglobin levels were not decreased. Serum haptoglobin may sometimes remain normal in patients who have mild hemolysis when an infection or a tumor coexists. It is known, however, that the lysis of only 20 ml. of blood will lower the haptoglobin level for several days. If hemolysis had caused the profound anemia in our patient, there should have been a decrease in haptoglobin. Furthermore, the hypocellular marrow obtained during the second hospitalization documented a hyporegenerative state consistent with the pancytopenia manifested by the patient.

We could surmise that a lack of folate or an iron deficiency might have contributed to the pancytopenia, as reported to occur in patients with chronic hemolytic
disorders who develop aplastic crises.\textsuperscript{2,9,15} Also, the bleeding within the tumor could have worsened the anemia, as shown by Price and associates.\textsuperscript{17} Furthermore, iron reutilization is impaired in patients who have neoplastic diseases.\textsuperscript{5} However, our patient's serum iron was never low, iron stores were demonstrable in her bone marrow, and a trial treatment with iron and folate failed to elicit a reticulocyte response.

Since the hematologic normalization occurred only after tumor excision, we attribute the pancytopenia manifested by our patient to a condition of bone-marrow failure caused by the granulosa-cell tumor. Others have found similar hematologic complications in patients with neoplasms. Law described pancytopenia with normocellular marrow in a case of squamous-cell carcinoma of the bronchus several months prior to the development of metastases.\textsuperscript{13} Pancytopenia, hypocellular marrow, and high serum iron levels with overall features of hypoplastic anemia were found by Banerjee and Narang in two patients who had malignant neoplasms who were not being treated by chemotherapy or

---

**Fig. 4.** Hematologic values before and after operation. Small arrows (\(\uparrow\)) indicate transfusions of erythrocytes. Circles (\(\bigcirc\)) represent units of platelet concentrate.
Fig. 5. Bone marrow smear nine months after operation. Cellularity is increased and megakaryocytes are adequate. Wright's stain. ×690.

other forms of treatment. About half the patients with pure erythrocytic aplasia harbor thymic tumors, and 25 to 30% experience remission of the anemia when the thymoma is removed.

We can only speculate on the pathogenesis of the bone-marrow failure shown by our patient. Although there is no proof, it is possible that an immunologic mechanism was involved. Immunoglobulins produced by tumor tissue may damage host erythrocytes, as described by DeBruyere, or coat nucleated erythroid marrow precursors and inhibit heme synthesis. Since erythrocytes, leukocytes, and platelets share common antigens, antibodies to erythrocytes may cross-react and destroy other cell types, either in the peripheral blood or centrally in the bone marrow.

So far as we could ascertain from a review of the literature, ours is the only recorded case of bone marrow failure in a patient with an ovarian tumor. We hope that this paper will stimulate further observations in similar cases.

References
7. Dawson MA, Talbert W, Yarbro JW: Hemolytic