Krukenberg's tumor in the young population

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Krukenberg's tumor secondary to gastric adenocarcinoma was identified in a 20-year-old woman. The patient died ten weeks after surgery, which included total hysterectomy, bilateral salpingo-oophorectomy, tumor debulking, and subtotal gastrectomy. Her unexpected advanced disease and fulminant course led the authors to review the literature for other reports of Krukenberg's tumor in the young person. However, the age category was not studied specifically in most series, and only a few cases involving patients of very young age were detailed. The present case appears to be only the fifth involving a patient aged 20 years.

In 1896, Frederick Krukenberg¹ described bilateral ovarian enlargements caused by secondary adenocarcinoma of the ovaries. Histologically, Krukenberg's tumor is composed of malignant, mucin-producing signet-ring cells in an abundant fibrous stroma.² Primary sites usually are the stomach or colon; less commonly, the breast, gallbladder, small bowel, pancreas, uterus, or urinary bladder harbors the primary cancer.²⁻⁴

The average age of patients with Krukenberg's tumor is 40 to 45 years, and the tumor rarely is seen in patients younger than 35 years.⁵ The patient in our case was 20 years old at diagnosis, and, thus, she was one of the youngest persons reported to have Krukenberg's tumor.

Report of case

A 20-year-old, nulliparous woman was admitted complaining of abdominal pain and increasing abdominal girth of three months' duration. There was no significant medical or family history.

The patient was 62 in tall and weighed 183 lb. Her blood pressure was 140/90 mm Hg, and she had a low-grade fever (temperature of 99.6°F). Facial hair growth was slightly increased. The abdomen was soft, distended, and tender. No masses were appreciated, and a fluid wave was possibly present.

The patient initially refused pelvic and rectal examinations because of her discomfort. Pregnancy and Papanicolaou's tests had negative findings. The erythrocyte sedimentation rate was elevated to 47 mm/h.

An upper gastrointestinal roentgenographic series revealed irregularity along the greater curvature of the stomach. Pelvic sonography and abdominal computed tomography revealed massive ascites, and bilateral, large, complex ovarian masses measuring between 7 cm and 9 cm as well as bilateral hydrothorax; these findings were consistent with Meig's syndrome. Barium enema study of the colon showed no abnormalities.

Laparotomy revealed the following abnormalities: (1) Bilateral, symmetric ovarian enlargement, with extensive involvement of peritoneum, omentum, and the se-

Fig 1. Excised Krukenberg's tumor, with bilateral ovarian enlargement.

rosal surface of abdominal organs; (2) a palpable gastric mass involving the greater curvature of the stomach; and (3) massive ascites (volume, 4 L). Total hysterectomy, bilateral salpingo-oophorectomy, debulking of the tumor, and subtotal gastrectomy were performed.

The excised ovarian tumor is shown in Fig 1. The histopathologic impression was that of gastric carcinoma, with bilateral ovarian metastasis and widespread involvement of omentum, peritoneum, and regional abdominal lymph nodes. The gastric neoplasm was consistent with primary adenocarcinoma (linitis plastica type), and the ovaries contained secondary adenocarcinoma with mucin-positive signet-ring cells (Figs 2,3). Ascitic and pleural fluids were positive for adenocarcinoma.

Fig 2. Signet-ring cells in ovary (hematoxylin and eosin stain; original magnification $\times 40$).

Fig 3. Signet-ring cells in ovary and large, pale mucous granules and dark, dense mucous granules (electron microscopy, original magnification $\times 30,000$).

Postoperatively, the patient's course was complicated by persistent, malignant pleural effusions and hypoproteinemia. Chemotherapy was withheld because of her poor medical status. She died approximately ten weeks after surgery.

Discussion

A computer search of the English medical literature back to 1938 revealed no studies of Krukenberg's tumor that dealt specifically with the age of patients. Most reports mentioned only broad age groups. Except in isolated reports and in Hale's⁵ series, it was difficult finding the exact age of each

patient. Only three patients as young or younger than our patient have been reported to have Krukenberg's tumor, with a fourth patient described only as "a young girl."^{3,6,8}

Gastric carcinoma in the young population was reviewed in two studies. In McNeer's⁹ series of 501 patients with gastric carcinoma who were younger than 31 years, 50 had Krukenberg's tumor. Exact ages, however, were not reported clearly in this study. Tamura and Curtiss¹⁰ identified 11 cases of ovarian metastasis from gastric primary carcinoma in patients younger than 36 years. Again, individual ages were not given. Table 1 reviews nine series^{3,5,7,8,11-15} of Krukenberg's tumor published in the past 50 years.

One of the more widely discussed series was published by Woodruff and Novak⁷ in 1960. In reviewing 1,700 cases recorded in the Ovarian Tumor Registry during a 17-year period, they found 48 cases of Krukenberg's tumor. The age range in the series was 16 to 61 years; however, individual ages were not provided. The authors state that the youngest patient was 13 years old, but the reference case is unknown. In this study, 80% of the patients had bilateral tumors and 50% of the patients had gross evidence of malignancy, with metastatic disease in the abdominal cavity.

The single largest study of Krukenberg's tumor (81 cases)

TABLE 1. KRUKENBERG'S TUMOR: PATIENT AGES, PRIMARY SITES, AND SURVIVAL DATA FROM NINE PUBLISHED SERIES.

Study date	Author(s)	No. of cases	Age		Primary site (No.)	Survival data
			Range (yr)	Mean (yr)		
1938	Novak and Gray ¹¹	21	22-60	42	Stomach (6) Colon (5) Unknown (10)	Follow-up in 17 of 21 cases. Death of 13 patients within six weeks to 14 months. Death imminent for three patients when last seen. Only one patient with presumed primary Krukenberg's tumor was alive and well after four years.
1951	Karsh ⁴	4	28-47	39	Stomach (3) Gallbladder (1)	Not discussed.
1956	Soloway et al ¹³	16	30-61	44	Stomach (9) Breast (4) Sigmoid colon (1) Unestablished (2)	Average survival time was 6.6 months. Longest survival was 28 months. One patient was alive after 24 months.
1960	Woodruff and Novak ⁷	48*	16-61	40	Stomach (19) Breast (4) Gallbladder (1) Colon (1) Undetermined (13) No other primary site identified (10)	Five patients lived four or more years; four of the five had a known primary site other than the ovary.
1968	Hale ⁵	81	21-81	45	Stomach (76) Breast (2) Sigmoid colon (2) Cecum (1)	One patient alive at 45 months. Longest other survival was 20 months. Death occurred at an average of 9.8 months from onset of symptoms and at an average of 7.1 months after diagnosis.
1968	Joshi ⁸	18†	16-61	38	Classified as primary Krukenberg's tumor (no other known primary site).	Survival was analyzed in nine cases. Four patients lived longer than five years (several days to 14 months longer).
1981	Bullon et al ¹⁴	13	29-84	47‡	Tubular Krukenberg's tumor Stomach (4) Sigmoid colon (1) Appendix (1) Undetermined (7)	Ten of 13 patients died with disseminated tumor from two to 21 months postoperatively (variety of surgical procedures). Two patients were alive without evidence of disease seven to nine months postoperatively.
1982	Holtz and Hart ³	27	20-70	46§	Stomach (16) Colon (4) Unknown (7)	Not discussed.
1986	Wong et al ¹⁵	15	30-72	44	Stomach (4) Breast (1) Ampulla of Vater (1) Colon (1) Unknown (8)	One patient was alive 34 months after bilateral oophorectomy.

* Includes Karsh and Soloway cases.

† Includes eight cases from Woodruff and Novak series.

‡ Six patients were 35 years old or younger.

§ Twelve patients were 40 years old or younger.

was by Hale,⁵ who studied the records of four major hospitals in Honolulu from 1945 through 1965. The patients ranged in age from 21 to 81 years; the average age was 45 years. Age distribution was made according to five-year groupings. Only two

patients were included in the 20- to 25-year-old group; seven patients were in the 26-to 30-year-old group, and six patients were in the 31-to 35-year-old group, for a total of only 15 patients (18.5%) aged 35 years or younger. There was a preponder-

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Brief Summary

FELDENE® (piroxicam) Capsules

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS: Peptic ulceration, perforation, and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS). Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms.

PRECAUTIONS: Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of piroxicam to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally, nephrotic syndrome.

A second form of renal toxicity has been seen in patients with preexisting conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly.

Because of extensive renal excretion of piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged), lower doses of piroxicam should be anticipated in patients with impaired renal function, and they should be carefully monitored.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

FELDENE (piroxicam) is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE at doses of 20 mg/day. Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress, nausea, constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion.

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia.

Dermatologic: pruritus, rash.

Central Nervous System: dizziness, somnolence, vertigo.

Urogenital: BUN and creatinine elevations (see PRECAUTIONS).

Body as a Whole: headache, malaise.

Special Senses: tinnitus.

Cardiovascular/Respiratory: edema (see PRECAUTIONS).

*Reactions occurring in 3% to 9% of patients treated with FELDENE. Reactions occurring in 1% to 3% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth.

Hematological: thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis.

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions.

Central Nervous System: depression, insomnia, nervousness.

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS).

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS).

Special Senses: swollen eyes, blurred vision, eye irritations.

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina.

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease.

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS).

Incidence Less Than 1% (Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancreatitis.

Dermatologic: onycholysis, loss of hair.

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias.

Urogenital System: dysuria.

Body as a Whole: weakness.

Cardiovascular/Respiratory: palpitations, dyspnea.

Hypersensitivity: positive ANA.

Special Senses: transient hearing loss.

Hematological: hemolytic anemia.

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis: It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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ance of Japanese patients in this series. The primary neoplasm site was the stomach in 76 patients (94%). The colon and breast were the primary sites in three and two cases, respectively. Sixty-seven tumors (83%) were bilateral. The largest ovary measured 22 cm. The average duration from diagnosis until death was 7.1 months.

More recently, Holtz and Hart³ analyzed a series of 27 typical Krukenberg's tumors in patients ranging in age from 20 to 70 years. The exact age of each patient was not reported in the study. It is only known that the youngest patient was 20 years old. One case was described as involving "a young girl." Three patients had had recent pregnancies. Pleural effusions were present along with pulmonary metastasis in several patients, and osseous metastasis was found in eight patients.

Krukenberg's tumor accounts for only 3% to 5% of ovarian tumors.^{3,7,13} As in our case, symptoms typically are abdominal pain and distention secondary to pelvic masses and gastrointestinal distress.^{2,3,5,7,14} The duration of symptoms prior to diagnosis is variable, but it averages 2.6 months according to Hale.⁵ With the preoperative workup often helpful only in identifying ovarian masses, the exact diagnosis frequently is not made prior to surgery.^{3,5,7,13,14}

At the time of diagnosis, the metastatic spread of tumor usually is extensive. Ascites, a prominent finding in our patient, has been reported in 46% to 64% of cases, and malignant pleural effusion has been found in about 8% of cases; both of these are regarded as poor prognostic signs.^{5,7} In Hale's⁵ series, the average duration of disease from the onset of symptoms to death was 9.8 months. Prognosis depends partially on the advancement of disease prior to diagnosis and treatment. Surgery appears to offer the most benefit to patients with less advanced disease, and when the tumor appears to be limited to the organs removed.^{2,6,7,16}

Although there is a dearth of information regarding Krukenberg's tumor in young patients, the typical characteristics do not appear to be altered by age. The peak age of Krukenberg's tumor patients (the fifth decade) is lower than that for gastric carcinoma (peak ages 55 to 65).^{1,12} Sixty percent of Krukenberg's tumor develop in patients who are still menstruating.¹³

Recent pregnancy and, occasionally, virilization are associated with the tumor.^{3,5,7,14} Because aggressive malignant metastatic disease frequently is seen in young persons, the patient's youth may obscure accurate diagnosis, because of the failure to suspect this secondary ovarian disease in the first three or four decades of life.^{9,10} It is important, therefore, to report and describe cases in young patients with this unusual tumor.

Summary

Krukenberg's ovarian tumor rarely is seen by the community hospital surgeon, and its diagnosis in a young woman with bilateral ovarian masses often is not made until laparotomy. Such was the case with our 20-year-old patient, who at laparotomy was found unexpectedly to have Krukenberg's tumor with diffuse metastatic disease.

In the recent literature, few cases of this tumor in such a young patient can be found for comparison. To our knowledge, there has been no reported case of Krukenberg's tumor in a woman this young since 1982, and this may be only the fifth documented case in such a young patient in the last 50 years.

Such cases should be reported so that more may be learned about the natural course and pathology of Krukenberg's tumor in young women and girls, and the tumor should be kept in mind as a differential diagnosis of bilateral ovarian masses.

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