Krukenburg Tumor Presenting in a Young Female with Rapidly Progressive Course and High-Frequency TP53 Mutation Burden

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Citation

C Parsa, R Murray, P Talbott, R Orlando. *Krukenburg Tumor Presenting in a Young Female with Rapidly Progressive Course and High-Frequency TP53 Mutation Burden*. The Internet Journal of Pathology. 2022 Volume 23 Number 1.

DOI: 10.5580/IJPA.56213

Abstract

The term Krukenberg tumor refers to ovarian adenocarcinoma with signet-ring cell features, most originating from the stomach. These tumors are aggressive, and diagnosis is often complicated in that the patients are usually asymptomatic until after metastasis. We present a case of a 19-year-old female, who initially presented with diffuse abdominal pain and was subsequently discovered to have bilateral Krukenberg tumors that had not been present on imaging studies eight months earlier. Next generation sequencing (NGS) revealed a clinically significant TP53 mutation in the ovarian metastases. The high TP53 mutation allele frequency of 65.8% in this patient's malignancy, warrants consideration of this mutational contribution to the patient's rapidly progressive course and its role as a germline (inherited) mutation. These patients may be candidates for early intervention with more aggressive therapeutic options and may benefit from genetic counseling.

INTRODUCTION

Krukenberg tumors (KTs), first described by Dr. Fredrich Krukenberg in 1896 are rare, primarily bilateral, metastatic cancers involving the ovaries. These neoplasms comprise approximately 1-2% of ovarian tumors. The most common primary site of cancer is stomach, but they can also metastasize from the colon, appendix, or breast. It is thought that the route of metastasis from the stomach to the ovary is via retrograde lymphatic spread. They are most common in the 4th to 5th decade of life, and in 20-30% of cases are preceded by a prior history of carcinoma [1].

While previous cases of younger patients with Krukenberg tumor have been reported, this case is notable for the high TP53 mutation allele frequency, unusual initial syncopal presentations, and its rapid progression from negative pelvic CT findings to metastatic cancer in only 8 months.

Mutations in the TP53 gene, a tumor suppressor that encodes the p53 protein, may result in loss of p53 function and increase the expression and stability of the altered p53 protein in the nucleus, sometimes leading to genomic instability, excessive cell proliferation, and carcinogenesis [2,3](34, 35, 36, 37, 38, 39). Considering the high mutation allele frequency, the possibility of a germline (inherited) TP53 mutation cannot be excluded. These patients may benefit from consultation with a genetic provider.

CASE REPORT

A 19-year-old female was brought via ambulance to urgent care for evaluation of 2 syncopal episodes. She had complained of one week of intermittent epigastric pain, with associated nausea and vomiting. She denied fever, chills, diarrhea, melena, hematochezia, hematemesis, vaginal bleeding, or hematuria. Her last menstrual period was one week earlier. A non-contrast Computerized Tomography of the abdomen and pelvis showed no abnormalities of pelvic organs. Endoscopy revealed a large cratered ulcer that was actively bleeding. Hemostasis was achieved with epinephrine, bipolar cautery and a hemoclip. The patient was then discharged after receiving two units of packed red blood cells with instructions to be followed by her gastroenterologist in 3 to 5 days.

The patient returned to the emergency department 8 months later following two syncopal episodes with a 2-week history of diffuse abdominal pain and associated nausea. She had a 2-month history of amenorrhea. She denied fever, chills, and recent trauma. Significant laboratory findings included the following: WBC, 7.5 x 109/L; RBC, 5.03 x 1012/L; Hgb

11.4 g/dL; Hct , 35.3 %; MCV, 70.1 fL; RDW, 20.4; serum ferritin, 7.3 ng/mL; serum albumin, 2.4 g/dL; total protein, 5.7 g/dL; TSH , 4.17 mIU/L; and CA-125, 127 units/mL (normal, 0-35). Other serum tumor markers (AFP, CEA, and beta hCG) were within normal limits.

Contrast CT of the abdomen and pelvis revealed presence of large amount of ascites and was concerning for two pelvic masses or a bilobed mass (Fig. 1). Soft tissue omental thickening was also present, possibly representing peritoneal metastasis. No focal lesions were seen in the liver, spleen, adrenal glands, or kidneys.

Open laparotomy was subsequently performed with bilateral salpingo-oophorectomy and biopsy of peritoneal implants for diagnostic purposes. The left and right ovaries were irregularly shaped, multinodular, 10 x 8 x 6 cm and 12 x 10 x 7 cm, respectively. Upon sectioning, the cut surfaces of the masses were solid fleshy pale tan without evidence of hemorrhage or necrosis. (Fig. 2)

Figure 1

Contrast CT of abdomen and pelvis showing 2 large masses at the level of the adnexa.

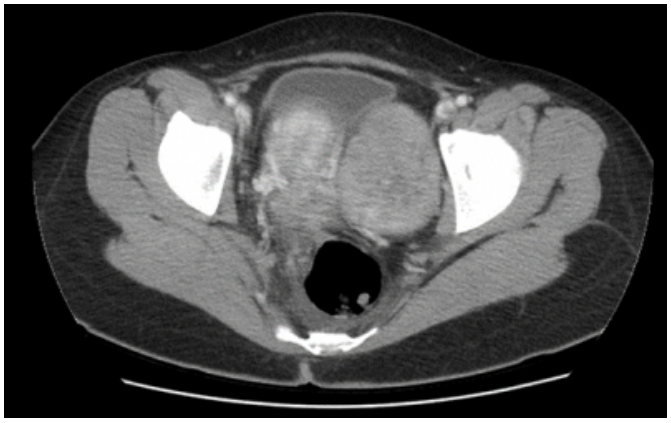
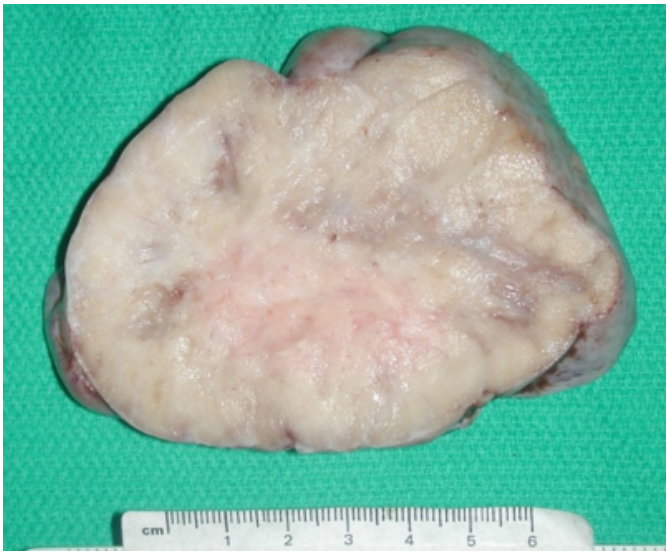


Figure 2

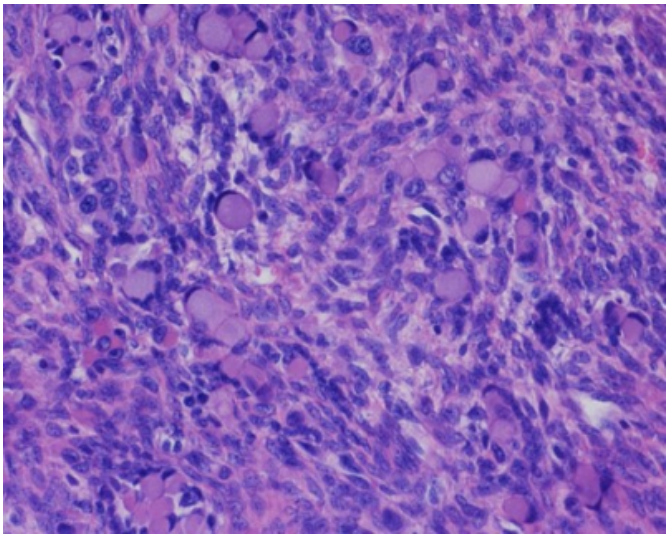
Cut section of the right ovarian mass showing solid tan surface without evidence of hemorrhage or necrosis



Histologic sections of the masses consisted of a poorly differentiated malignant neoplasm with variable spindle and signet ring cell features (fig. 3). Sections of the peritoneal biopsy showed similar pathologic findings.

Figure 3

H&E stain of the mass showing poorly differentiated malignant neoplasm with variable spindle cell and signet-ring cell features.



Immunohistochemical (IHC) stains were variably positive for CK 7, CK20 , and E-cadherin, but negative for GATA-3 and vimentin. The tumor cells were [2]positive for special stains periodic acid Schiff (PAS), Alcian Blue (pH 2.5) and mucicarmine.

The histopathologic and IHC findings were consistent with metastatic adenocarcinoma, originating in the stomach.

An EGD, performed subsequently, showed a large infiltrative lesion in the proximal lesser curvature of stomach and biopsied. The histomorphologic findings were confirmatory for a poorly differentiated adenocarcinoma with signet ring features (figures 4 and 5). There was also gastric mucosal ulceration with severe chronic inflammation.

Figure 4

H&E stain of stomach biopsy showing poorly differentiated adenocarcinoma with signet ring features.

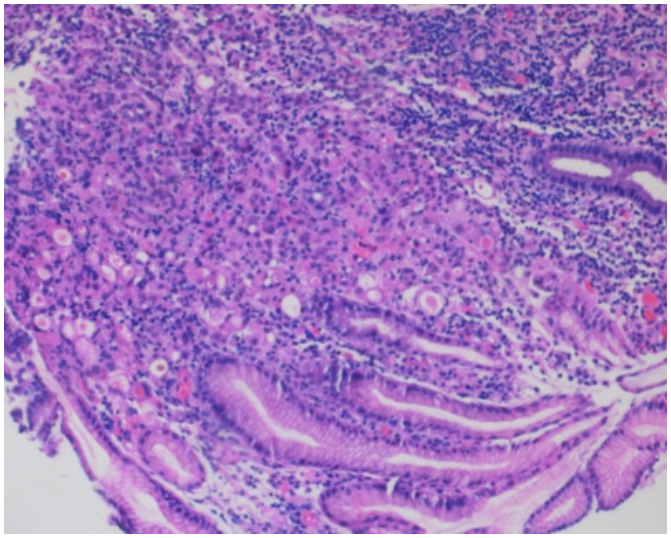
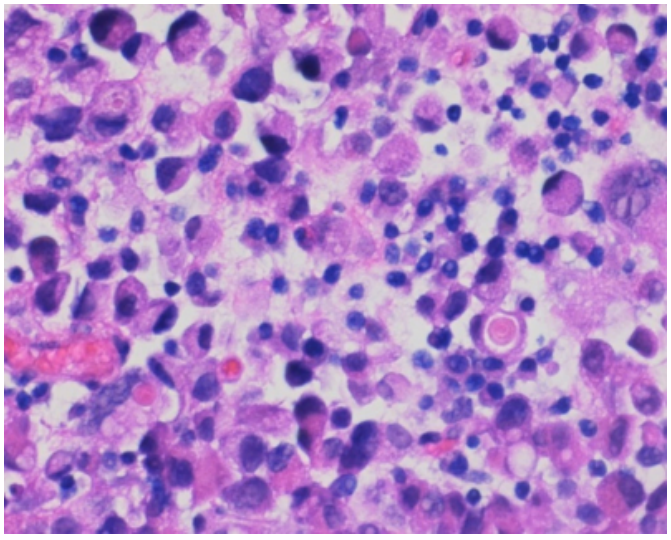


Figure 5

gastric Signet ring cells highlighted at higher magnification



Ancillary IHC biomarker studies of the tumor were negative for Her2/neu, IDH-1, p16, p53, and PDL-1. The tumor cells exhibited intact nuclear expression for all four mismatch repair proteins.

Next generation sequencing was significant for the detection of mutant allele TP53 splice site c.375+1G>A with high-frequency (65.8%), as well as microsatellite instability (MSI) results showing stable microsatellites (MSS), with low tumor mutation burden (5.3 Mutations/Mb)

DISCUSSION

Krukenburg tumors are often asymptomatic until after metastasis, complicating timely diagnosis. These tumors grow quickly, with an average of 6 months between diagnosis of the primary carcinoma and the ovarian involvement. In a retrospective study of 128 patients, the prognosis for these highly malignant tumors is often poor, with an average survival of just 16 months[4]. Prognosis is worsened if the primary tumor remains undetected.

These tumors often mimic most common primary ovarian mass lesions by imaging studies. They may also share histomorphologic features with a benign ovarian signet ring stromal cell tumor. These primary ovarian stromal tumors show a conspicuously different IHC panel: positive for vimentin and negative cytokeratins [5]. Also, Metastatic gastric signet ring tumors are more likely to be bilateral and produce mucin, which can be easily visualized using special stains (e.g. PAS or mucicarmine) or by immunohistochemistry (e.g. vimentin and EMA)[5,6].

Patients with ovarian cancers often present with vague symptoms and primary versus metastatic cancers are often challenging differential diagnostic considerations. These patients are also at risk for development of additional cancers[6]. TP53 mutation, considered an early event in the gastric tumorigenic process, has been described in 50% of primary gastric cancers, and up to 70% of metastatic cases[7]. Patients with primary serous ovarian cancers may also show TP53 mutation[8] and must be differentiated from those with Krukenberg tumor. At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches currently under investigation, however, include gene therapy for TP53 and dendritic cell-based TP53 vaccines[9,10], Wee1 inhibitor adavosertib (MK-1775) and Aurora kinase A inhibitors are other therapeutic approaches under investigation for TP53-mutated cancers[11,12].

In view of this patient's young age and rapid progression with development of ovarian metastases within a short time,

it may be warranted to recommend early determination of TP53 status in the course of these patients disease and consider a more aggressive approach in the available therapeutic options. Also, high-frequency TP53 mutations are considered germline mutations and as such genetic counseling may be useful in these patients[13].

Declaration of Competing Interest

The authors state that they have no competing interests or financial incentives.

References

1. Al-Agha, O. M. & Nicastri, A. D. An In-depth Look at Krukenberg Tumor: An Overview. Arch. Pathol. Lab. Med. 130, 1725–1730 (2006).
2. Wang, Y.-C. et al. Wild-type p53 overexpression and its correlation with MDM2 and p14ARF alterations: an alternative pathway to non-small-cell lung cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 23, 154–164 (2005).
3. Sood, A. K., Sorosky, J. I., Dolan, M., Anderson, B. & Buller, R. E. Distant metastases in ovarian cancer: association with p53 mutations. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 5, 2485–2490 (1999).
4. WU, F. et al. Clinical characteristics and prognostic analysis of Krukenberg tumor. Mol. Clin. Oncol. 3, 1323–1328 (2015).
5. DeCoste, R. & Offman, S. L. Signet Ring Stromal Cell Tumor: A Legitimate (Benign) Mimic of Krukenberg Tumor. Arch. Pathol. Lab. Med. 142, 1289–1291 (2018).
6. Powers, J. et al. A Rare *TP53* Mutation Predominant in Ashkenazi Jews Confers Risk of Multiple Cancers. Cancer Res. 80, 3732 (2020).
7. Cr□ciun, M. I. & Domşa, I. Immunohistochemical diagnosis of Krukenberg tumors. Romanian J. Morphol. Embryol. Rev. Roum. Morphol. Embryol. 58, 845–849 (2017).
8. Oien, D. B. & Chien, J. TP53 mutations as a biomarker for high-grade serous ovarian cancer: are we there yet? Transl. Cancer Res. 5, (2016).
9. Vermeij, R. et al. Immunological and clinical effects of vaccines targeting p53-overexpressing malignancies. J. Biomed. Biotechnol. 2011, 702146 (2011).
10. Saito, H. et al. A combined lymphokine-activated killer (LAK) cell immunotherapy and adenovirus-p53 gene therapy for head and neck squamous cell carcinoma. Anticancer Res. 34, 3365–3370 (2014).
11. Kato, S. et al. Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. Proc. Natl. Acad. Sci. U. S. A. 100, 8424–8429 (2003).
12. Olivier, M. et al. Recent advances in p53 research: an interdisciplinary perspective. Cancer Gene Ther. 16, 1–12 (2009).
13. Mitchell, G. et al. High Frequency of Germline TP53 Mutations in a Prospective Adult-Onset Sarcoma Cohort. PLOS ONE 8, e69026 (2013).

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