Krukenberg tumor in an 11-year-old girl

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\textbf{Abstract}

Krukenberg tumors are uncommon metastatic neoplasms of the ovary with a prominent component of signet ring cells. The occurrence of a Krukenberg tumor in young individuals is rare, with only few cases reported in the second decade of life. The authors describe a case of this tumor diagnosed in an 11-year-old girl, characterized by massive metastatic spread, lack of tumor response and rapidly fatal clinical course. To the best of our knowledge, this is the youngest patient with Krukenberg tumor reported to date.

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Metastatic involvement of the ovaries is not a rare event in adult cancers and 5–30\% of ovarian cancers are metastatic malignancies\textsuperscript{[1]}. Approximately 5\% of all carcinomas metastatic to the ovaries are adenocarcinoma with pleomorphic mucin-filled signet-ring cells, firstly reported by Friedrich Ernst Krukenberg in 1896, and therefore named Krukenberg tumor\textsuperscript{[2]}. In this tumor, the most frequent site of the primary is the stomach (70\% of the cases), followed by large bowel, appendix and, occasionally, a variety of other locations\textsuperscript{[1,3]}. However, in a quarter of the cases, the primary tumor is very small and can escape detection. The involvement of the ovary, which is most commonly bilateral and can reach huge proportions, is thought to be the consequence of selective retrograde lymphatic spread of the primary tumor along the stomach-ovarian axis\textsuperscript{[4]}. Since no effective treatment has been identified, patients diagnosed with Krukenberg tumor usually have a fatal outcome, with a median survival time of 14 months\textsuperscript{[5]}. In this report, we describe the case of a girl who was diagnosed with Krukenberg tumor at the age of 11 years. To the best of our knowledge, this is the youngest patient with this particular tumor reported to date.

\textbf{1. Case report}

On December 2011, an 11-year-old girl developed asymptomatic swelling of the prepubic soft tissues, that was considered of inflammatory nature by the family pediatrician and was consequently treated with antibiotic and anti-inflammatory medications without appreciable response. Four months later (28 of March, 2012), due to the extension of the swelling to soft tissues of both upper thighs and the appearance of severe generalized pain, the patient was referred to our institution. On admission, she appeared to be in pain but in good general condition, the only abnormal finding being the swelling described above. Abdominal ultrasonography and magnetic resonance imaging revealed diffuse thickening of the prepubic and upper thighs soft tissues and two huge, round solid masses, almost entirely occupying the pelvic cavity (Fig. 1a), interpreted as tumor involving and obliterating both ovaries. In addition, multiple skeletal lesions, particularly involving some vertebrae and the iliac bone, and enlarged mediastinal lymph nodes, were observed. Positron emission tomography confirmed the lesions described above, and showed irregular
uptake of the radionuclide at the level of both lung bases arising the suspicion of their metastatic nature. The results of the laboratory work-up were within normal limits, with the exception of slightly elevated serum levels of CA 19.9 38.9 U/ml (normal values 0.0–37.0), CA 125 73.26 U/ml (normal values 0.0–37.0) and chromogranin A 48.0 U/L (normal values 2.0–18.0). At exploratory laparotomy (performed on April 3, 2012), the impression derived by the imaging of a massive tumor possibly destroying the ovarian tissue was confirmed. Based on the hypothesis that the ovarian function was lost, following achievement of parental consent, resection of both masses together with bilateral salpingectomy was carried out without difficulties, due to the absence of adhesions of the masses to the neighboring organs and tissues. Neither tumor deposits nor ascites were observed upon exploration of the abdominal cavity. The masses measured 15 × 10 × 6.5 cm and 10.5 × 5.5 × 4 cm in diameter, respectively. Their external surface was bosselated, while the cut surface was solid, multinodular, soft to firm in consistency, and pale-yellow in color (Fig. 2a,b). Microscopically, the masses showed the same morphology made of ill-defined nodules, trabeculae and small tubules, embedded in a fibro-edematous stroma. The cells had eccentric hyperchromatic nuclei and cytoplasm from granular eosinophilic to pale vacuolated (signet ring cells) (Fig. 2c). PAS and mucicarmine stains revealed the presence of mucin in the cytoplasm of these cells. Focal necrosis and prominent lymphatic permeation were both observed. The neoplastic cells showed immunoreactivity for CKpan, CK7, CK20, EMA and only focally for CEA (luminal) and chromogranin. A diagnosis of signet ring cell carcinoma, seemingly metastatic, was made.

Following an uneventful post-operative course, investigation in search of a possible primary tumor was undertaken, which included breast and thyroid ultrasound, esophageal gastro-duodenal and ileum colorectal endoscopy, hysteroscopy, exploratory laparoscopy with appendectomy. All failed to identify abnormal masses or tissues. Upon consultation with an adult oncologist, chemotherapy was initiated using the association of taxol and carboplatin [6]. Two courses were administered starting on May 23 and June 13, 2012, respectively. During this treatment, progressive worsening of clinical conditions and intense generalized bone pain occurred. A total-body computed tomographic study was performed on July 10, 2012, and showed massive enlargement of the mediastinal and cervical lymph nodes, and diffuse edema of both lungs with lower pulmonary micronodularity suggesting carcinomatous lymphangitis (Fig. 1b). A dramatic pattern of multiple organ failure intervened in the following days leading to the patient’s death on July 12, 2012, three months after diagnosis. Parents denied permission for autopsy.

2. Discussion

Krukenberg tumors are rare (1–2% of ovarian tumors) [1,4]. The age of patients with this tumor ranges from 13 to 84 years with a lower median compared to other ovarian neoplasms (41–45 years vs 55–65) [5,7]. In the largest series of Krukenberg tumors
(120 cases) described by Kiyokawa et al. in 2006, four (3%) were diagnosed in the second decade of life, including a 13-year-old adolescent. The primary site in these 4 patients was unknown in 3 and was defined “nongastric” in the fourth one [7]. The authors found two other cases described in the literature, which had occurred decades before, in adolescents with primary in the sigmoid colon and stomach, respectively [8,9]. Finally, a 13-year-old patient with primary in the sigmoid colon was recently described, although her outcome is not reported [10].

Our patient was 11-year-old at the time of diagnosis and therefore represents the youngest case of Krukenberg tumor reported to date. She presented with swelling of abdominal wall and upper thighs soft tissues, which was interpreted as a consequence of retrograde lymphatic spread, the mechanism by which the Krukenberg tumor is thought to be established [5]. Imaging work-up revealed the possibly effacement of both ovaries by the tumor. The positivity of serum tumor markers supported the carcinomatous nature of the lesions. The fact that the ovary may occasionally give origin to a variety of epithelial tumors even in the adolescent has long been known [11]. However, the massive involvement of both ovaries was rather in favor of the metastatic nature of the lesion, a condition almost unknown in pediatric oncology. The suspicion of Krukenberg tumor was taken into consideration, despite the lack of reports describing this tumor in the pediatric age range, but clearly required histological verification. The post-operative work up failed to detect a primary tumor, as occurs in a quarter of Krukenberg tumors, whereas it unexpectedly revealed massive metastatic involvement of the skeleton.

Treatment of Krukenberg tumor includes resection of metastases and of the primary tumor, commonly located in the gastrointestinal tract. However, the primary often remains undetected, as occurred in our case [7]. Chemotherapy was therefore the main treatment modality for our patient, although its effectiveness is poorly established. The association of carboplatin and taxol was chosen based on the consideration that the ovarian origin for our patient’s tumor could not be excluded, and that platinum compounds represent the first line treatment for upper gastrointestinal tract tumors. Furthermore, taxanes are indicated in the treatment of advanced breast and thyroid cancers and are active in undifferentiated neoplasms. Finally, the use of an association of drugs with a large spectrum of activity seemed to be the right treatment choice for a metastatic tumor of unknown origin [6]. The attempt turned into a failure, as the tumor underwent rapid fatal progression.

The dramatic clinical course of our adolescent patient represents an additionally impressive feature of this report. Whether the patient’s young age may have a negative impact on the clinical course of Krukenberg tumor has not been investigated. However, in 1986, Gupta et al. described a twenty-year-old patient, who presented with advanced disease and had a fulminant course. They hypothesized that Krukenberg tumor may have an especially aggressive course in the young population [12].

3. Conclusion

In summary, the case described herein, together with a few others previously reported in adolescence, indicates that the ovary could be the site of massive metastatic spread, showing the typical features of Krukenberg tumor, even at this age. Although this must be considered an exceptional finding, we believe that this rare condition should be included in the differential diagnosis of pediatric ovarian neoplasms.

Conflict of interest statement

The authors declare no conflicts of interest.

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