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PEDIATRIC GASTOINTESTINAL AND OVARIAN LYMPHOMA: EXTENSION OF THE CLASSICAL KRUKENBERG TUMOR PHENOTYPE

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ABSTRACT

Objectives: Originally, Krukenberg tumor was described as a selective spread of cancer, most commonly in the stomach-ovarian axis, of epithelial tumors, in mid-age or elderly women. The objectives are to describes, for the first time, the youngest three girls with gastrointestinal lymphoma and ovarian dissemination and to expand the non-epithelial krukenberg tumor phenotype.

Material: Three girls, 9, 14, 15 years old, presented with abdominal pains, anemia, elevated acute phase reactants, were diagnosed with terminal ileum, gastric and colonic lymphoma spreading to their ovaries. The youngest girl had liver metastasis and the older one multiple organ spread. The two youngest girls had Burkitt while the 15 years old had large B cell lymphomas.

Results: All were treated by anti lymphoma chemotherapy and only the youngest girl was operated, and bone marrow transplanted. Prognosis is favorable, two are considered cured and one in remission.

Conclusions: The present pediatric cases extend Krukenberg tumor concept, for the first time, to include the pediatric age group and add Burkitt and non-Burkitt lymphoma to the list of non epithelial tumors in the intestinal-ovarian axis. The medical community and especially gastroenterologist, gynecologist and oncologist should be aware of the presently described unique manifestation.

KEYWORDS: Gastrointestinal Tract, Krukenberg Tumor, Lymphoma, Ovary, Pediatric

INTRODUCTION

Krukenberg tumor (KT) is an uncommon metastatic tumor of the ovary, described originally in 1896 by Friedrich Krukenberg, a German gynecologist and pathologist [1]. Classically, KT refers to a metastatic ovarian malignancy whose primary site arose in the gastrointestinal tract. Stomach is the primary site in most KT cases (70%), carcinoma of colon, appendix, and breast follow [2-5]. Rare cases of KT originating from carcinomas of the gallbladder, biliary tract, pancreas, small intestine, ampulla of Vater, cervix, renal pelvic/ urinary bladder/urachus, liver and even leukemia were described [2-13]. From the pathological aspect, adenocarcinoma composed of signet ring cells of various organs tend to metastasize to the ovaries much more commonly than adenocarcinomas of other histological types from the same sites [2, 4, 6, 13], gastric one is the most common example. The average age of patients with KT is 40-45 and the tumor is rarely seen in

patients younger than 35 years [14]. Moreover, till 1989, only 4 classical KT girls below the age of 18 years, were described [15]. Lymphoma can be rarely, a primary or metastatic tumor of the ovaries [16-18]. Of 75 ovarian tumors investigated for their primary site, 12% were lymphoma [16]. Of 40 cases of ovarian lymphoma examined, 10 were small noncleaved cell lymphoma (undifferentiated Burkitt's and non-Burkitt's) [18]. Nevertheless, the first description in the medical literature of a non-Hodgkin, diffuse large B cell lymphoma with synchronous involvement of stomach and ovary was in a 61 years-old woman [19]. None were described in the pediatric age-group

Three girls, with gastrointestinal lymphoma, spreading to their ovaries, are described, for the first time. The cancer-type and the group age, extend the classical KT phenotype and call the medical community to be aware of the presently described unique manifestation.

Subjects

Case 1

14 years old girl was admitted because of abdominal pain and dysuria accompanied by fever for few hours. One month before, urea breath test was performed because of epigastric pain and was positive for Helicobacter pylori. On admission, physical examination revealed a mass in RLQ of the abdomen. Laboratory analysis: mild microcytic anemia: Hb 11.8 g/dl, MCV 74fl, CRP 75mg/L, LDH 653IU/L. The following examinations were within normal limits: biochemical profile, urine spot and culture, fibrinogen, alfa feto protein, CA-125/15-3/19-9, carcino-embrionic antigen, coagulation test, blood count except for the anemia. On

Gynecologic examination a RLQ mass was palpated and pelvic US revealed two large masses. The only abnormalities on CT of the abdomen were gastric wall thickening with a large mass in the gastric fundus and two large ovarian masses measuring 11X5.3 cm on the left and 9.6X3.4 cm on the right. On gastroscopy: 7-10 cm size mass occupying the lower half of the great gastric curve with a central necrotic ulcer was observed. On pathology, the gastric biopsies from the mass, disclosed Burkitt lymphoma. Using immunohistochemistry, the neoplastic cells were positive for: CD20, CD79, BCL-6, CD10 and negative for: CD3, CD56, Cyclin D1, Tdt, and CD34. Ki-67 proliferation index was 100%. Gastric biopsies beyond the mass showed antral mucosa with chronic inactive helicobacter pylori gastritis.

The child was treated according to the LMB protocol, Group B which includes: Cyclophosphamide, Doxorubicine Methotrexate, Vincristine, Steroids and responded very well to the first course, entered complete remission after the third course. She did not develop severe complications except for mucositis grade 3. The gastric and ovaries tumors disappeared. She is now in complete remission for 3 years since the end of therapy, PET-CT is strictly normal.

Case 2

A 9 years old girl presented with abdominal pain. Her past history was unremarkable. Physical examination revealed a right lower quadrant abdominal palpable mass. Laboratory analysis: Hb 12.7 gr%, leucocytes 9100/ul, platelets 510.000/ul, LDH 720 IU/L. Pelvic US showed an infra-hepatic mass of 8cm diameter, a right ovarian mass of 6 cm dimension and multiple hepatic lesions, suspected for metastasis. CT of the abdomen revealed the mass in the right ovary, an additional mass in the right flank, of 8cm diameter and liver metastases. On abdominal laparatomy the surgeon performed excision of the mass in the right flank, right ovarectomy and biopsies of the liver metastases. The histological diagnosis of the abdominal mass and ovarian was malignant diffuse small non cleaved Burkitt's type lymphoma. Bone marrow and lumbar puncture were normal

The girl received chemotherapy including Cyclophosphamide, Doxorubicine, Methotrexate, Vincristine and Steroids. Restaging was normal but she developed severe toxicity from Methotrexate and severe candidemia and did not succeed to end the whole protocol. Therefore, a high dose chemotherapy with autologous bone marrow transplantation was performed. She did not develop any severe complications during the transplantation. Nowadays, she is 32 years married + 2 children and considered fully cured.

Case 3

A 15 years old girl, presented with upper abdominal pains, weight loss and lower back and sacral pain irradiating to the left thigh, for one month duration. Physical examination revealed only sacral tenderness, thyroid enlargement and jaundice. Laboratory work-up disclosed iron deficiency anemia (Hb 10.4 gr%), transaminasemia (SGOT 396u/l, SGPT 272u/l) and cholestatic jaundice (D/TB 11.27/11.6mg/dl). Abdominal US showed diffuse enlargement of the pancreas and biliary tree dilatation. Abdominal CT reassured the US findings and added a sacral space occupying lesion. Bone scan disclosed a left sacral uptake.

On chest CT, the thyroid looked diffusely enlarged. Endoscopic US was normal. Total body Pet-CT disclosed pathological uptake in the following organs: total enlarged pancreas, sub hepatic portal lesion of 2.2 cm diameter, dilated biliary tree, ascending colon wall enlargement, left upper abdomen mesenteric fat infiltration, pelvic lesion of 6.4x10 cm dimension, involving the two ovaries and the surrounding peritoneum and a lymphatic node in the left external iliac chain of 2.3 cm diameter. In the skeleton, increase uptake was notice in: the right distal and left proximal humerus, right acromion, right anterior 1st rib and left ileum wing. A big mass, of 11cm length, involving the whole sacral length, mainly on its left side, with cortex destruction and left neurological foramina involvement, was noticed.

The following laboratory examinations were within normal limits: complete blood count, biochemical profile, CEA, CA-19-9, Thyroid functions and TPO, HAV, HBV, HCV serology, coagulation profile. LDH was elevated (620IU/L) on admission. A CT-guided per-cutaneous sacral biopsy revealed large B cell lymphoma diffusely positive for CD20 and CD79a immunostaining. The diagnosis of LMB group C, stage four was established. She was treated according to the LMB protocol, Group C including: Cyclophosphamide, Doxorubicin, Methotrexate, Vincristine, Steroids, ARA-C and Etoposide without any major complications. Actually she is 21 years old and considered cured. All three women signed an inform consent.

DISCUSSIONS

Historically, KT is named after Friedrich Ernst Krukenberg (1871-1946), a German gynecologist and pathologist, who first described it as "fibrosarcoma ovarii mucocellular carcinomatodes"[20]. Since then, the multi-facets phenotypes of the original KT were expanded considerably. The organs involved, the histology, age range and the hypotheses for the routs of matastasis spreading along the intestinal-ovarian axis were changed. Concerning the histology of the invading cancer, the original description of mucin-secreting signet-ring cells was evolved considerably and some other pathological features were added. Microscopically, KT has two ovarian components: epithelial and stromal. The epithelial component is composed chiefly of mucin-laden signet ring cells with eccentric hyperchromatic nuclei. However, KT can display a predominantly tubular pattern, where the signet ring cells are present in tubules and intermingled with stromal cells. The mesenchymal component of KT is of ovarian stromal origin. Sometimes, the stromal reaction is so intense that it obscures the signet ring pattern, rending its diagnosis challenging, and possibly confused with fibromas [2]. Recently,

some new pathological presentations were added to the classical KT. Glandular, fibrolaminar, mucinous cacinoid-like, cellular-acellular pattern, B cell lymphoblastic leukemia and large B cell lymphoma were described [4, 7, 8, 9, 19]. It can be deducted, actually, that the original histological features of KT were expanded and include a wider variety of pathological patterns.

The peak age of KT patients is the fifth decade, commonly seen in middle-aged and elderly females around or following menopause. Sixty percent of the women are still menstruating. Reviewing 120 KT, women ages ranged from 13 to 84 years (average 45 years) with 43% of them under 40 years [6]. Along the time, the age-range distribution turned toward a younger age. In fact, till 1989, 5 classical KT girls below the age of 20 years were described [15]. More recently, in large series, few young females were added [4, 6, 21]. It can be summarized that also in the age-range aspect, age of presentation of KT is shifted to a younger age, with time.

Pathophysiologically, the rout of matastasis along the intestinal-ovarian axis is also evolving. Classically, it was thought that direct seeding across the abdominal cavity account for the spread of the tumor. Latter, hematogenous spread was suggested and it is now evident that retrograde lymphatic spread is the most likely route of metastasis as there are several evidences supporting this concept [2, 22].

The girls, currently presented, shed new light on the classical KT. They are unusual in their age distribution as well as in the pathology of their tumors. The second case is the youngest, in the literature, having KT. All the three were below the age of 18 years, at the time of diagnosis.. Burkitt lymphoma was never described in KT. The only description of lymphoma, in the KT literature, is a case of non-Hodgkin, diffuse large B cell lymphoma, in a 61 years old woman [19]. Compared to recent study on B-cell non-Hodgkin lymphoma prognosis in children and adolescents, the present serie had favorable out come and good prognosis [23, 24].

Several common features exist in the three girls, presently described: abdominal pain is the most frequent presenting symptom, imaging techniques like US and CT are very informative, gastrointestinal and ovarian distribution of the lymphomas simultaneously appeared, anemia and elevated acute phase reactants, anti-lymphoma chemotherapy is the treatment of choice, prognosis is very good.

Traditionally, the diagnosis of KT, along the years, was according to the World Health organization diagnostic criteria [25]. However, the term KT was also clinically defined as any ovarian metastatic carcinoma derived from a primary malignancy, thus adopting a more relative loose clinical definition [3,26,27]. Based on the current knowledge, the new aspects and the expunction, over the years, of KT, it is suggested that the description should be renamed and changed to Krukenberg syndrome. A syndrome is "the combination of signs and symptoms associated with a particular morbid process, which together constitute the picture of a disease"[28]. The literature, since the original description of KT, in 1896, changed extensively, concerning signs and symptoms. The terms adenocarcinoma of the stomach, mucin-secreting signet-ring cells, middle-aged and elderly females around or following menopause, should be expanded to many other organs, pathological processes and age –range. Even the routs of metastasis from the primary organ to the ovaries evolved to the lymphatic network. The present pediatric serie, further shows the wide variability of the signs and symptoms of the Krukenberg syndrome and adds two new aspects, namely, the pediatric age and the Burkitt and large B cell lymphomas. The medical community and especially gastroenterologists should be aware of the presently described unique manifestation.

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