Colonic adenocarcinoma and bilateral malignant ovarian sex cord tumor with annular tubules in Peutz-Jeghers syndrome

Adenocarcinoma del grosso intestino e sex cord tumor bilaterale ovarico maligno con tubuli anulari nella Sindrome di Peutz-Jeghers

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Key words
Peutz-Jeghers syndrome • Malignant transformation • Ovary • Sex cord tumor with annular tubules

Case report

A 46-years old woman was admitted for rectal bleeding, pelvic pain and extreme fatigue. In the last five months, she suffered from a left pelvic pain, vomiting, a bloody diarrhoea and weight loss. Past medical history and family history were unremarkable. The physical examination revealed besides a melanotic pigmentation of the lips and buccal mucosa, a painful solitary and irregular mass in the right upper quadrant. Serum alpha-fetoprotein (AFP) was 1190 UI/L. The serum level of CA-125 and CEA were not elevated. Colonoscopy showed an unbridgeable irregular bulky mass and a pedunculated polyp measured 1.5 cm and...
located at 15 and 12 cm respectively of the anal margin. The histological examination of the endoscopic biopsy of the colonic tumor showed a poorly differentiated adenocarcinoma. Abdominal and pelvic ultrasonography showed multiple echogenic liver nodules in segment II, IV and VI. The ovaries were enlarged, with ecogenic bilateral solid tumours of 35 mm and 30 mm in diameter. At laparotomy, a recto-sigmoidal tumor, a left ovarian mass and multiple liver metastases were found. A left hemicolectomy with colorectal anastomosis and bilateral ovariectomy were performed. Biopsy of hepatic lesions was done. The gross examination of the colonic resection demonstrated a multilobular polyploid mass measuring 4 x 3 cm diffusely infiltrating the wall extending to the serosal surface. A sessile polyp of 0.5 cm and a pedunculated polyp of 1 cm were seen near the colonic tumor. The left ovary measured 4 x 3 cm and showed at cut section tumor of 2.5 cm in diameter with both solid and cystic pattern. The right ovary measured 4 x 3.5 cm in size and its cut surface was yellowish gray or yellow and solid with cystic area. Microscopic examination of colonic tumor confirmed a poorly differentiated adenocarcinoma conserving the branching structure of smooth muscle (Fig. 1). Some tubular glands with cribriform pattern lining by atypical cells with high mitotic activity were observed (Fig. 2). There was no evidence of adenomatous change. Three mesocolonic lymph nodes showed metastatic deposits. The tumor cells stained strongly with cytokeratin and CEA but not for inhibin and AFP. Both polyps show similar features as characterized by core of smooth muscle fibres in a tree-like pattern with hyperplasia of the epithelium (Fig 3). Many glandular structures exhibited abnormal branching patterns; others were cystically dilated. The microscopic appearance of both ovaries was similar and consistent with sex cord tumor with annular tubules (Fig. 4). Both simple and complex annular tubules with prominent basement membranes were present. The cells were round with pale abundant often lipid-rich cytoplasm, and showed little nuclear atypia and few mitoses. These cells form outlined nests surrounded by hyaline layers and containing eosinophilic hyaline bodies typical of annular tubules. Components of Leidig cells were found at the periphery of the tumor. Immunohistochemical study shows positivity for estradiol, progesterone and inhibin, and a focal stain for AFP (Figs. 5, 6). However, tumor cells were negative for CEA. Biopsy of liver lesions yielded clusters of cells with consistent cytologic changes noted from the sex cord tumour with annular tubules.

The post-operative course was uneventful. The patient was then placed on a chemotherapy regime consisting of a combination of bleomycin, cisplatin and etoposid. Six months later, her general condition was good, and upper gastrointestinal endoscopy revealed no polyp in the stomach and the duodenum. The patient’s liver lesions were significantly smaller and the initially elevated AFP levels decreased during the course treatment.
Discussion

The PJS is an autosomal dominant disease with variable expression and incomplete penetrance of LKB1/STK11 gene at chromosome 19p13.3 encoding for a novel 433-aminoacid serine threonine kinase. Recently an increasing number of reports underline the neoplastic potential of this syndrome and it is now believed to increase the risk of developing gastrointestinal cancers, predominantly occurring in the duodenum and also the colon, and extra-intestinal malignancies particularly ovarian. There still remains the controversy as to whether gastrointestinal cancer in the PJS arises from the Peutz-Jeghers polyps, or de novo. Former conclusions concerning the risk and pathogenesis of cancer in the PJS may be provided by prospective studies. However, the small number of patients with this syndrome and the long interval between diagnosis of the syndrome and the appearance of cancer are obstacles to such studies. But many epidemiological factors have led to the hypothesis of cancer arising in Peutz-Jeghers polyps: young age of the patients at the diagnosis of cancer, increase of gastrointestinal cancer’s risk (eighteen times greater than expected in the general population) and reports of gastrointestinal cancers in families involved with PJS. In the last few years, many histological arguments have been reinforcing the hypothesis of a “hamartoma-dysplasia-carcinoma” sequence, in particular the presence of high dysplasic areas in the hamartomatous polyps and the presence of branched out strips of a smooth muscle within gastrointestinal carcinomas. In our case, the absence of adenomatous lesion in the colonic tumor, and the presence of smooth muscle fibres, contiguous to carcinomatous glands, are in-keeping with the hypothesis of cancer arising in a hamartomatous polyp. Recently, several investigators have reported that gastrointestinal cancers occur more frequently in PJS than described previously, and the incidence has been reported to be more than 10 percent.

In 5 to 14% of cases, the PJS is also associated to ovarian tumors, especially the sex cord tumor with annular tubules, which would be an almost constant finding in patient’s ovaries with this disorder, justifying a careful examination by multiple ovarian biopsies. This unusual tumor represents 0.05 to 0.6% of all ovarian neoplasia and is associated in one-third of cases with the PJS. The natural history and appropriate management of this tumor are unknown. According to the WHO, the SCTAT is presumed to be a variant of sex cord stromal tumour. This tumour appears to arise from granulosa cells, although the growth pattern resembles that of Sertoli cells. The absence of germ cells and karyotypic abnormalities led to eliminate gonadoblastoma. The SCTAT associated with PJS, is essentially benign and is often an incidental finding, which is grossly typically bilateral, multifocal and small, with areas of calcification. Histological features consist of on simple and complex tubular formations. Immunohistochemical
study is positive for vimentin intermediate filament, progesterone, testosterone and oestrogen receptors. Inhibin and Mullerian-inhibiting substance (MIS) proved to be effective markers. The ACE and the CA125 are both negative.

Our case is uncommon because of the production of AFP that was reported in rare cases of Sertoli-Leydig tumour associated with elevation of AFP serum. Based on these histological observations, it appears that SCTAT is a sex cord/stromal tumour made up of cells with differentiation in the direction of Sertoli cells rather than granulosa cells. Malignant behavior in SCTAT has heretofore been reported only in sporadic cases. To our knowledge, only one case of malignant SCTAT associated to the PJS has been reported in the literature. The main diagnosis of malignancy in SCTAT’s has been because the tumour has metastasised or recurred. Usual spread is to pelvic lymph nodes and supraclavicular lymph nodes, although it can spread to liver, peritonum and other organs. In our case, hepatic biopsy demonstrated that the liver lesions are metastatic SCTAT rather than metastatic colorectal carcinoma, and confirmed the malignant potential of ovarian tumour. Histological characteristics and the immunohistochemical phenotyping of both colonic and ovarian cancers were consistent with sex cord tumour with annular tubules let to exclude ovarian metastases of the colonic tumor. Our case is the first patient report to have a bilateral malignant SCTAT secreting AFP and Peutz-Jeghers polyposis and an adenocarcinoma of the colon probably arising in a Peutz-Jeghers polyp. It is particularly interesting because of this association and the AFP detected in this ovarian neoplasia.

Taking into account the above, we recommend a full gynaecological and gastro intestinal regular check up with endoscopic resection of any gastro intestinal polyp with histological examination is required in case of PJS. This protocol may improve the prognosis and allow a better understanding of the exact mechanism of malignant transformation of hamartomatous polyps.

References