Synchronous serous peritoneal carcinoma and infiltrating mucinous appendicular adenocarcinoma. Immunohistochemical and molecular study.

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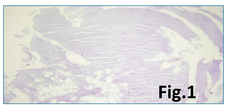
CASE REPORT: 67y old woman with a strong family history of ovarian and breast cancer that had increased CA125, CA53 with normal CEA. TC scan showed ascites with peritoneal carcinomatosis without adnexial abnormalties. Laparoscopic exploration demonstrated a mucinous perforated appendicular tumor with scarce extraappendicular mucin and many peritoneal implants with macroscopic normal ovaries. Biopsies were taken from the periappendicular mucin and from peritoneal implants.



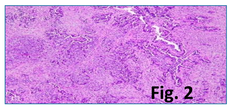
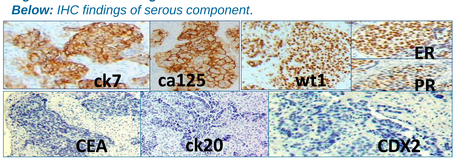


Fig1: *acellular mucin.* ***Fig 2:*** *serous carcinoma.*
Below: *IHC findings of serous component.*

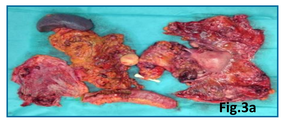


Microscopy and molecular studies: Periappendicular sample turned out to be acellular mucin material (**Fig 1**) while peritoneal implants (**Fig. 2**) showed infiltrating carcinoma with an immunoprofile characteristic of serous carcinoma, positive for ck7, Ca125, WT-1, ER, PR and negative for ck20,CDX2, CEA and Ca19.9 (Fig 2). However KRAS mutational studies showed different results in the acellular mucin component and in the serous carcinoma with presence of G12D KRAS mutation in the mucin and no abnormalities in the carcinoma component.

BRAF was wild type in both components. Taken all this information into account we considered the possibility of two synchronous neoplasias: a mucinous tumor with probable appendicular origin and a peritoneal/ovarian serous carcinoma.

Treatment: Patient received neoadjuvant chemotherapy with a partial response and negativity of serum tumor markers, so a cytorreduction surgery was done with resection of pelvic peritoneum, hysterectomy with double annexectomy, appendicectomy and extirpation of all macroscopic tumoral implants (**Fig 3a**.)

Microscopy and molecular studies : The appendix showed a mucinous adenoma with an adenocarcinomatous component on the tip with mucin extrusion (**Fig 3b**). All serosal implants (appendicular, peritoneal, mesocolon, bilateral ovarian surface) were classic serous carcinoma (**Fig.3c**).
Focally, both components were admixed (**Fig. 3d**).



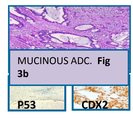
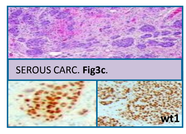
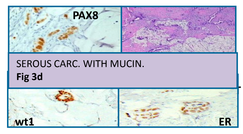


Fig. 3a *Spleen, uterus with double annexectomy, omentectomy and intestinal resection with tumoral implants.*
Fig. 3b and c *Mucinous and serous carcinomas.* ***Fig. 3d*** *Serous carcinoma admixed with mucin.*





Tables 1 and 2 show immunohistochemistry and molecular results.

Table 1 IHC RESULTS	CK20	CK7	Ca125	CEA	CDX2	p53	ER/ PR	WT1	PAX8
Appendicular mucinous adc.	+	+	+	+	+	+	-	-	-
Serous carcinoma	-	+	+	-	-	-	+	+	+

Table 2 MOLECULAR STUDIES	KRAS	BRAF	18q	17p
Acellular mucin	GD12	WT	Not done	Not done
Appendicular mucinous adc .	GD12	WT	LOH	LOH
Serous carcinoma	WT	WT	WT	WT

DISCUSSION: The morphology, mutational studies, and immunoprofile confirmed the presence of two synchronous and different neoplasms: an appendicular mucinous adenocarcinoma and a high grade serous carcinoma.

Mucinous appendicular tumors. Malignancy in these tumors is defined by the presence of invasive glands in the extraappendicular component. In 4-20% of cases they are associated to other neoplasias in colon and ovary (always mucinous tumors) and they are considered to be the origin of pseudomyxoma peritonei. Typically they have the same molecular alterations (KRAS and TP53 mutations) and similar immunophenotype to colonic adenocarcinomas except for the positivity to ck7. LOH of 18q and 17p are frequent .

High grade serous carcinomas are considered to be originated in the tubaric epithelium or in the tubaric/peritoneal junction. They have a high genetic inestability and are agressive neoplasms. KRAS and BRAF are usually negative in contrast to benign and border line serous carcinomas. The immunoprofile is characterized by positivity to WT1, PAX8 and ER/PR. It is the subtype related to familial forms of ovarian and breast cancer with inactivation of BRCA1 and BRCA2. Our patient had a strong family history suspicious of harboring one of these mutations.
The coexistence of these two types of carcinoma is exceptional, and in that particular case, the presence of KRAS mutations in the acellular mucin helped to make the right diagnosis already in the first biopsy.

CONCLUSION: Probably the presence of residual nuclear material from the mucinous adenocarcinoma was detected by the molecular technique which demonstrates the high sensitivity of molecular methods and its potential role in the routine diagnosis in a general pathology laboratory.