CASE REPORT

On a Complex Biphasic Neoplasm Involving the Ovary and Omentum Expressing Neuroendocrine Markers, HBME1 and TTF1: A Case Report and the Literature Review

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ABSTRACT

A Case of Malignant Mixed Ovarian Tumor (OMMMT) with synchronous mesenteric localization presenting heterologous expression of neuroendocrine markers, mesothelin and TTFI is studied. The peculiarity of this case is that of presenting immunophenotypic characters not yet reported in the literature in OMMMT.

Key Words: Please add 3-8 keywords

1. INTRODUCTION

Primary Mullerian Mixed Malignant Tumors of the Ovary (OMMMT), otherwise defined as Mixed Malignant Mesodermal Tumors or Carcinosarcomas, represent less than 1% of all ovarian neoplasms and on the morphological level faithfully repeat the homologous uterine neoplasms. Neoplasms with these characteristics have also been described as primitive in the area of the Secondary Mûllerian system (peritoneum), sometimes synchronous with as many primitive Mûllerian Tumors in the genital area (Uterus, salpinx, ovary). The literature also reports very rare cases of MMMT expressing neuroendocrine markers, always, however, in the uterus. The literature does not report any case of ovarian MMMT expressing neuroendocrine markers.

2. CASE PRESENTATION

A 76-year-old woman was complained of abdominal pains and disorders of the intestinal transit for a few months. The laparoscopic investigation highlighted an ovarian left mass with a diameter of about 3 cm and a plaque swelling of the same size in correspondence with the greater omentum. There is only a modest peritoneal effusion. Biopsies are performed on both sides.

2.1 Materials and methods

The material is represented by two distinct specimens respectively labeled as ovary and peritoneum. Each sample is made up of some tiny cylindrical fragments of about 20 mm. long. The material is fixed in formalin and embedded in paraffin. Sections stained with hematoxylin and eosin are prepared. Other sections are subjected to immuno-histochemical investigation with the following antibodies: Vimentin, CD56, TTF1, HBME1 (Mesothelin), CD56, Synaptophysin, EMA, Cytokeratin 8-18, Chromogranin, CD117, DOG1, CD34, NSE, CA125, CDX2, INIBIN, KI67.

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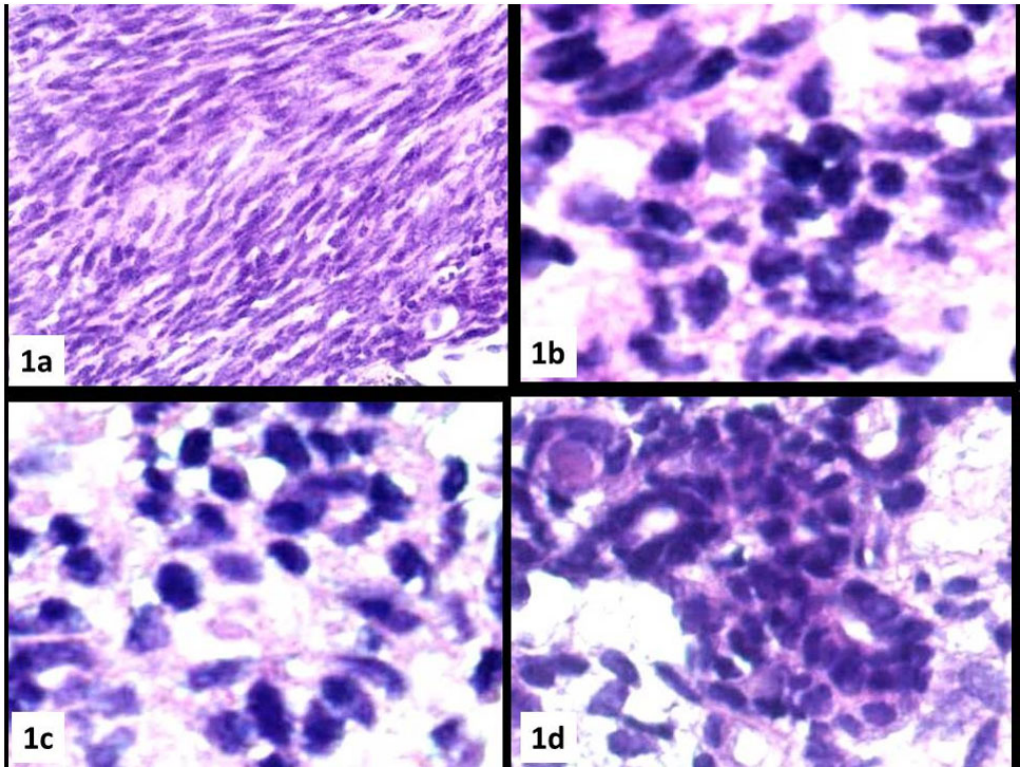

Figure 1. (Ovarian neoplasm. (a) Spindle cell component; (b) component with globose cells; (c) initial formation of a glandular lumen; (d) glandular lumens. H.E. 250 X

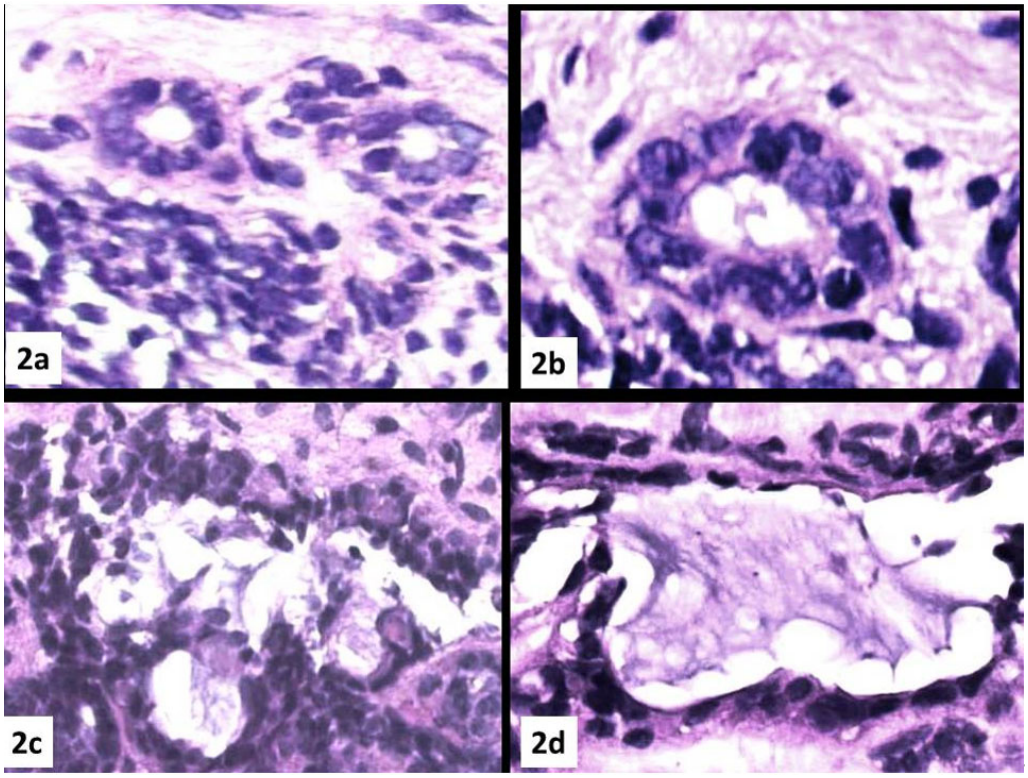

Figure 2. a-b. Glandular formations. Note the morphological identity of the cells lining the glandular lumens with the globose cells of the stroma; c-d. Glandular lumens containing basophilic mucoid material.H.E. 250 X

2.2 Histopathological Investigation

The morphological pattern of the material of ovarian origin and that of peritoneal provenance is substantially superimposable. It is a highly cellular proliferation made up of elements of globose or spindle-shaped form, provided with a bulky hyperchromatic nucleus and scarce cytoplasm(see Figures 1(a),1(b), 3(a),3(b)). The spindle elements, separated by a scarce stroma, tend to run parallel, sometimes assuming a vorticoid pattern. Globose, on the other hand, gathers to give rise to glandular lumens sometimes containing basophilic mucoid material(see Figures 2,3(a),3(b)). Mitotic activity is not noticeable. The results of the immunohistochemical investigation are reported in the following Table 1.

Table 1. The results of the immunohistochemical investigation

	VIM	CK8 -18	EMA	CD 56	CHM GR	SYNA PTO	NSE	TTF1	HBM E1	CD- 10	CD- 34	INIB -IN	Calr- et	KI- 67	CA1- 25	DO- G1	CD -X2	WT1	CD- 99
	+	+	+	+	0	+	+	+f	+	+f	0	0	0	>3 %	0	0	0	0	0
Figure	5a,.b	4a,.b	4 c, d	6a		6 c	6b	6d	7a, b, c,d	5 c, d									

On the basis of the morphological picture and Immunohistochemical Investigation, the diagnosis is made of Mixed Mûllerian Malignant Tumor of the Ovary and Peritoneum expressing Neuroendocrine Marker Mesothelin and TTF1.

3. DISCUSSION

Mûllerian Malignant Mixed Tumors (MMMT) are biphasic neoplasms, composed of morphologically malignant epithelial and stromal elements. The stromal component can be homologous, i.e. composed of elements of the endometrial (or ovarian) stroma, or heterologous when elements with rhabdomyoblastic, chondroblastic, or osteoid characters are also present. The epithelial component may be serous, endometrioid, or poorly differentiated.[1] They can arise in any genital organ, but are more frequently present in the endometrium where they represent less than 5% of malignant neoplasms; they can also arise, in the cervix, ovary, fallopian tube, and, rarely, the peritoneum. In the ovary, they represent less than 1% of all malignancies. They occur preferably in postmenopausal women and are usually diagnosed at an advanced stage.[2–4]

The immunophenotypic pattern of these tumors is characterized by the constant and widespread expression of epithelial antigens (Cytokeratin and EMA) and stromal (Vimentin). Nuclear expressivity for TTF1 is reported in all benign and malignant Müllerian tumors, with particular evidence in MMMT.[5]

The literature reports rare cases of neuroendocrine expression in cancers of the female genital tract. In endometrial adenocarcinoma.[6, 7] MMMT with neuroendocrine expressiveness is reported in the uterine cervix (2 cases) and peritoneum (1 case),[8–10] No cases of OMMT expressing neuroendocrine markers are reported in the literature.

The case of our observation presents a double localization of the tumor: in the ovarian and peritoneal sites. In the literature, both cases of extragenital MMMT with peritoneal localization and cases of peritoneal and genital synchronous neoplasms have been reported.[11] Regarding the synchronous or metachronous presentation of peritoneal MMMT with another tumor, a review of 16 cases reports 6 ovarian, 2 endometrial, 1 cervical, 3 tubal, and 3 colonic locations, of these 50% were synchronous.[12] In this series, there is no case of synchronous localization of MMMT in the peritoneal and ovarian sites as in our observation. This association makes it very likely that one of the two lesions is metastatic.

Both ovarian and omental lesions express focal, but intense, HBME1 (Mesothelin). Expression of Mesothelin is reported in ovarian tumors, and precisely in 81% of serous adenocarcinomas, in 50% of endometrioid and NOS, while it is constantly unexpressed in mucinous tumors. No case of OMMMT expressing HBME1 is reported .. The expression of Mesothelin is considered of crucial importance as it would favor the process of metastasis towards the peritoneum. An anti-mesothelin antibody would have shown therapeutic efficacy in reducing metastatic diffusion.[13]

As for the histogenesis of these intriguing neoplasms, numerous theories have been formulated over time. 1) Theory of collision: two different independent neoplasms that occur in the same territory; 2) Theory of combination: both neoplasms originate from the same stem cell; 3) Theory of conversion: sarcomatous cells derive from carcinoma; 4) Theory of composition: sarcomatous cells would be a pseusarcomatous reaction to carcinoma.

Thus, uterine carcinosarcomas should be regarded as metaplastic carcinomas and adjuvant treatment should probably be similar to that directed against aggressive high-grade endometrial carcinomas, rather than being sarcoma based are true collision tumors and this is important because the prognosis can sometimes be better than for a similar stage carcinosarcoma".[14]

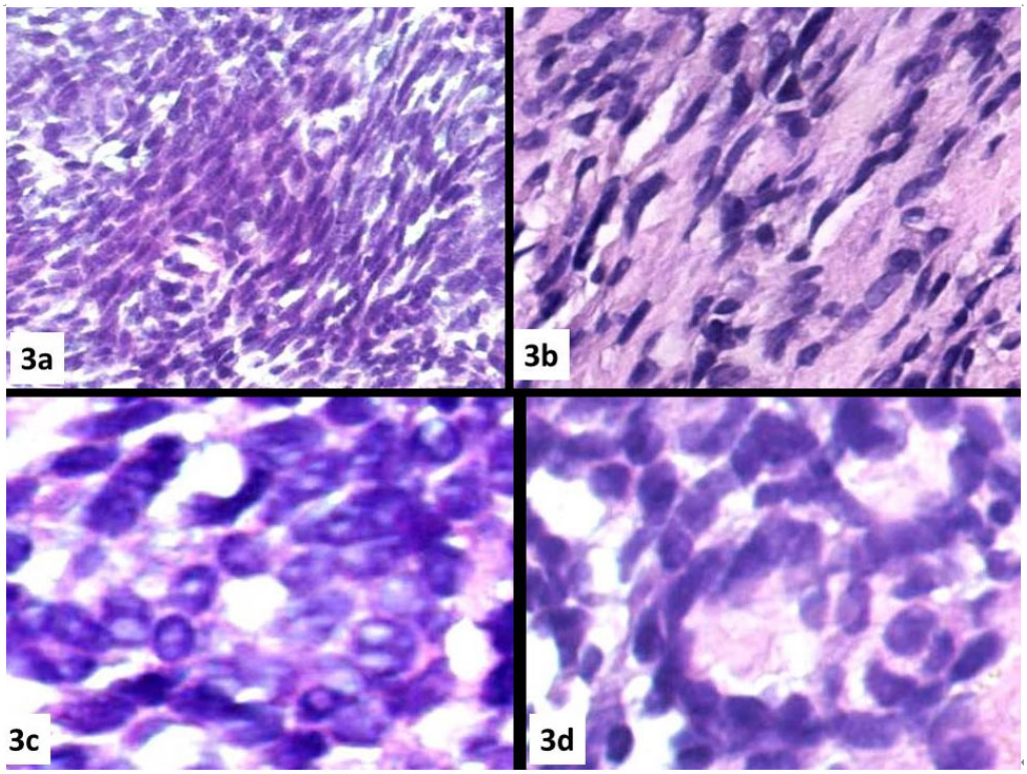

Figure 3. Omentum neoplasm. -a-b-c-d) Note the cytomorphological identity with ovarian neoplasm H.E. 250 X

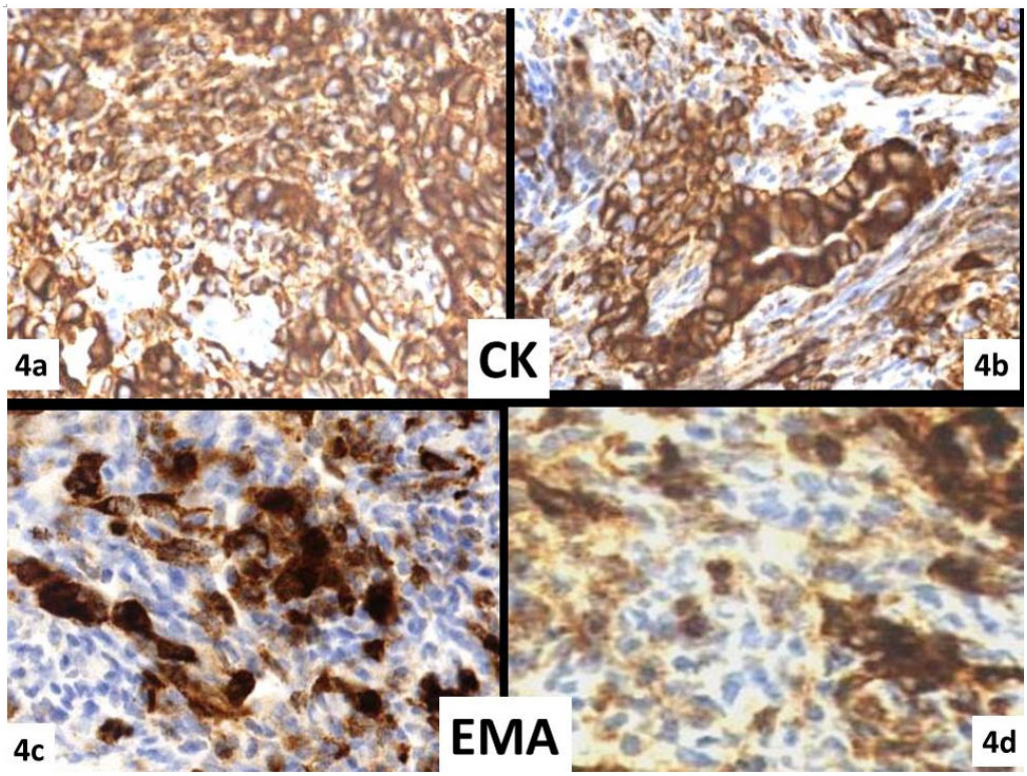

Figure 4. CK 8-18. a. positvity in stromal cells; b. positivity in glandular cells; c-d. EMA focal positivity. 250 X

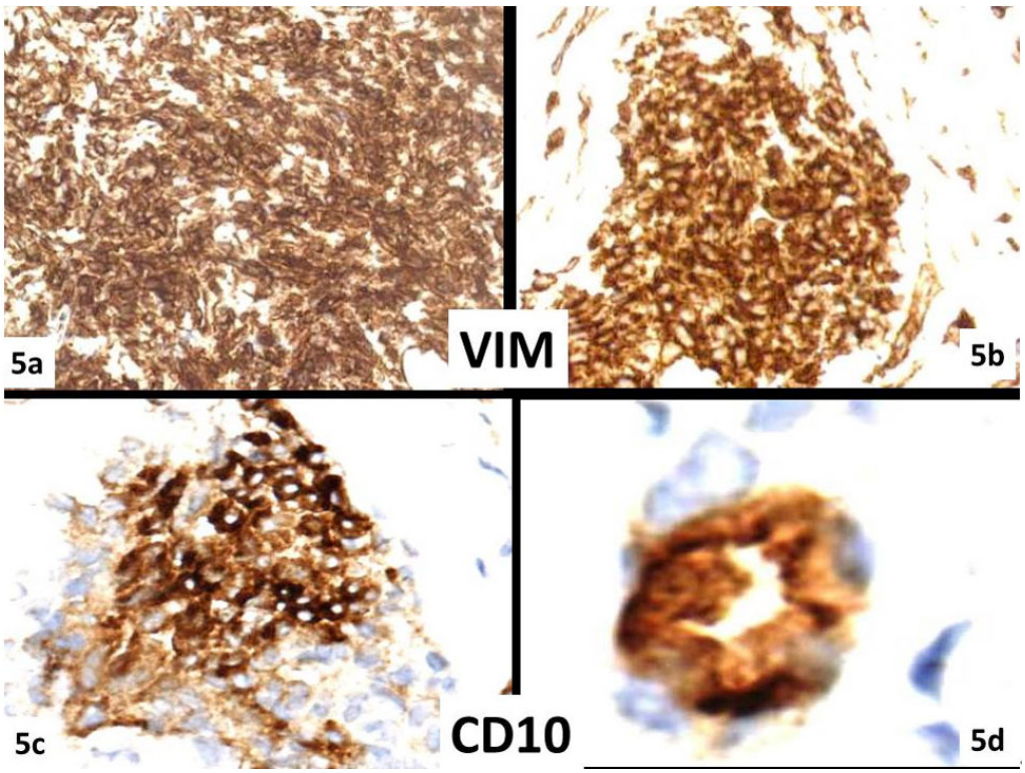

Figure 5. Vimentin. a. neoplasm ovary ;b. neoplasm omentum; c. CD10 neoplasm ovary, stroma; d. CD10 neoplasm ovary, glandular differentiation. 250 X

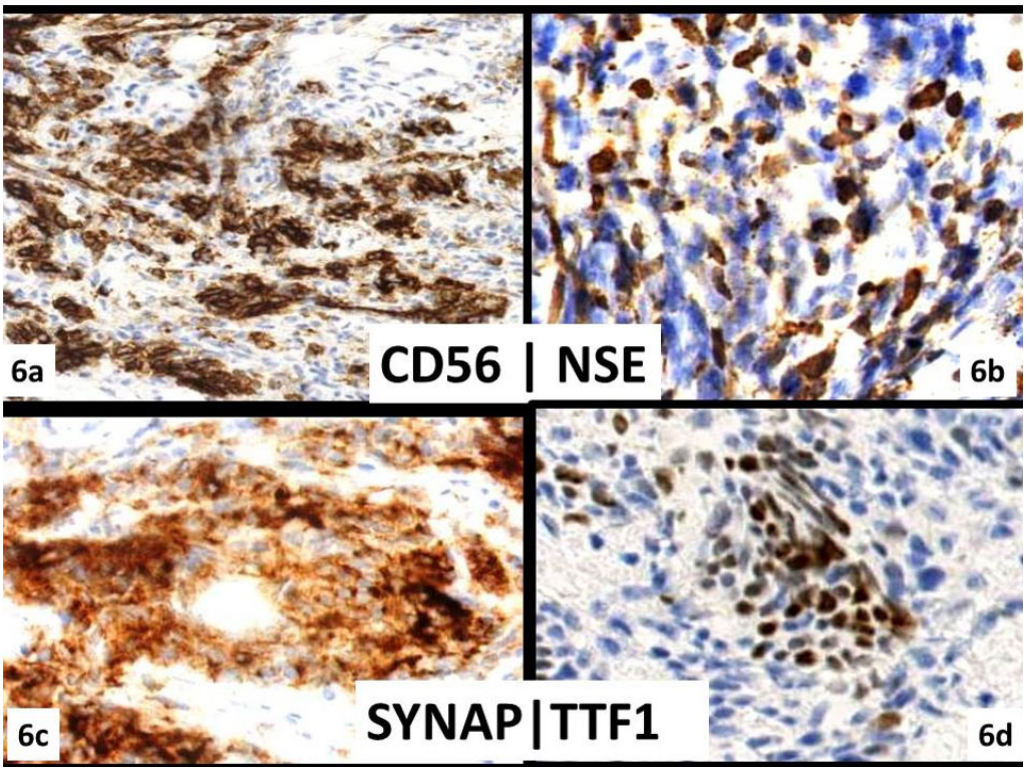

Figure 6. Neoplasm ovary . a. CD56; b. NSE;c. Synaptophysin; d. TTF1 (focal) . 250 X

4. Conclusions

The case study shows many peculiarities. On a morphological level, it is a biphasic neoplasm quite different from the classic MMMT, whose glandular component is endometrioid, serous, or mucinous. In our case, the glandular structures are much less differentiated and seem to consist of the same elements of the stroma which aggregate giving rise to the formation of the glandular lumens.

The immunophenotypic profile shows concurrent expression of epithelial and mesenchymal antigens (CK, EMA, Vim.) (Figs 4a-b-c-d,5a-b) which confirms the mesodermal nature of the neoplasm and demonstrates that both the stromal and glandular components originate from the same cellular matrix. The focal expression of CD10 indicates the presence of an endometrioid stromal component which also participates in the formation of glandular lumens (Figs.5c-d,)

The expression of neuroendocrine markers is not currently reported in the literature in the OMMMTs (Figs. 6 a-b-c), as is the expression of TT F1(Fig.6d). The Mesothelin expression (Figs 7 a-b-c-d), as the literature reports, is an indicator of the propensity to metastasize in the peritoneum, but it is also an indication of the possibility of target therapy.

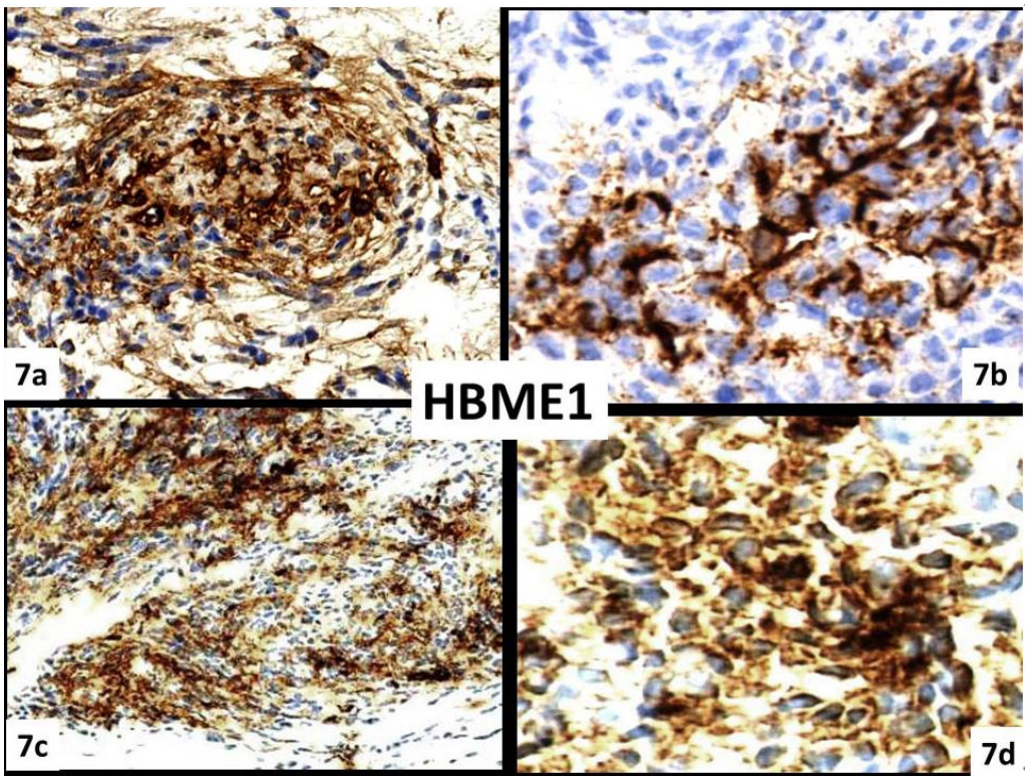

Figure 7. Mesothelin. a-b. Neoplasmo ovary; c-d. Neoplasm Omentum. 250 X

From the study of this case, it emerges that the various morphological aspects seem to be generated by a single cellular stem. It also emerges that in this type of tumor, in addition to the possibility of expressing heterologous tissue components (chondro, osteo, rabdo) there is also that of expressing heterologous immunophenotypes (Neuroendocrine Markers, TTF1)

Conflicts of Interest Disclosure

There is no conflict of interest.

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