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Hepatoid carcinoma of the ovary – A case report and literature review

Ana Karla Uribe Rivera[a,*], M. Alvarez Larraondo[b], L. Taxa Rojas[c], M. Bravo Taxa[d], A. Zevallos Cardenas[b]

[a] Resident of Surgical Oncology at National Institute of Neoplastic Diseases (INEN), Lima, Peru
[b] Department of Gynecological Oncology at National Institute of Neoplastic Diseases (INEN), Lima, Peru
[c] Department of Pathology at National Institute of Neoplastic Diseases (INEN), Lima, Peru
[d] Fellow of Oncological Pathology at National Institute of Neoplastic Diseases (INEN), Lima, Peru

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ABSTRACT

We present the case of a 27-year old female with an ovarian tumor and alpha-fetoprotein (AFP) of 1210 ng/m, a right salpingo-oophorectomy was performed and had conservative complementary staging by gynecologic oncologists. The histopathological report was primary hepatoid carcinoma of the ovary (HCO), clinical stage IA, complementary treatment was adjuvant chemotherapy with BEP and remains clinical, imaging and biochemically disease free in three years follow up.

1. Introduction

Hepatoid carcinoma of the ovary (HCO) is a very rare group of extrahepatic aggressive tumors with similar hepatocarcinoma (HCC) clinical and pathological characteristics, unknown histogenesis, and most frequent in postmenopausal patients. This histopathologic variant is classified by some authors within the epithelial origin of ovarian tumors, however, there is still controversy about its origin. HCO was first reported in 1987 Ishikura and Scully (Ishikura and Scully, 1987), who carried out a review of rare undifferentiated ovarian tumors, and found 5 cases with hepatocellular morphology and histologic characteristics without liver injury, 38 cases have been reported to date.

2. Case presentation

A peruvian 27-year old female, childless, referring three months with pelvic pain, she had an abdominopelvic ultrasound reporting right adnexal mass. It was operated in her hometown on January 2016, performing right salpingo-oophorectomy. The pathology report was epithelioid malignant neoplasm suggestive of undifferentiated ovarian carcinoma, annex size was 10 cm and serum alpha fetoprotein (AFP) of 1210 ng/ml, for what it was referred to the National Institute of Neoplastic Diseases (INEN).

On admission, physical examination was normal, new reading plates was performed and reports: Primary hepatoid carcinoma of ovary (Fig. 1), fallopian tube without pathologic alterations or tumor involvement, ovarian capsule neoplasm free. No evidence of endodermal sinus component. Immunohistochemistry PANKERATIN (+), AFP (+), GLYPICAN (+), HER PAR 1 (+), SALL-4 (focal+) (Fig. 1).

ABDOMINAL MR was made in March 2016 and report right annex absent, rest unchanged. Tumor markers: AFP: 10 ng/ml, Ca125: 10.05 U/mL, Ca19.9: 7.77 U/mL, CEA: 0.69, hCG < 0,100 mIU/mL. For surgical indication, it was known that the staging need to be completed, however we took into account the age and desire to procreate of the patient, the possibility of disease recurrence was explained, and the final decision was a conservative surgical ovarian staging by laparoscopy on April 2016 (peritoneal cytology, bilateral pelvic lymphadenectomy, paraaortic lymphadenectomy, infracolic omentectomy and peritoneum biopsies). Pathology report: multiple biopsies and omentum negative, 0/19 pelvic lymphadenectomy and 0/6 retroperitoneal lymphatics. The clinical stage was IA, and tumor markers were negative after surgery. A multidisciplinary meeting was performed for determinate adjuvant treatment in an early stage case with complementary conservative surgery without active disease. At the time of the present case (2014), our country did not have the SALL-4 study and the decision of chemotherapy was like a germ cell tumor, based on age of presentation and tumor markers.

Began adjuvant chemotherapy at 12 weeks' post-surgery, with three courses BEP (bleomycin, etoposide and platinum) culminating in November 2016, remaining under observation with negative imaging studies and tumor markers nowadays.

* Corresponding author.
E-mail address: karla.uriberivera@gmail.com (A.K. Uribe Rivera).

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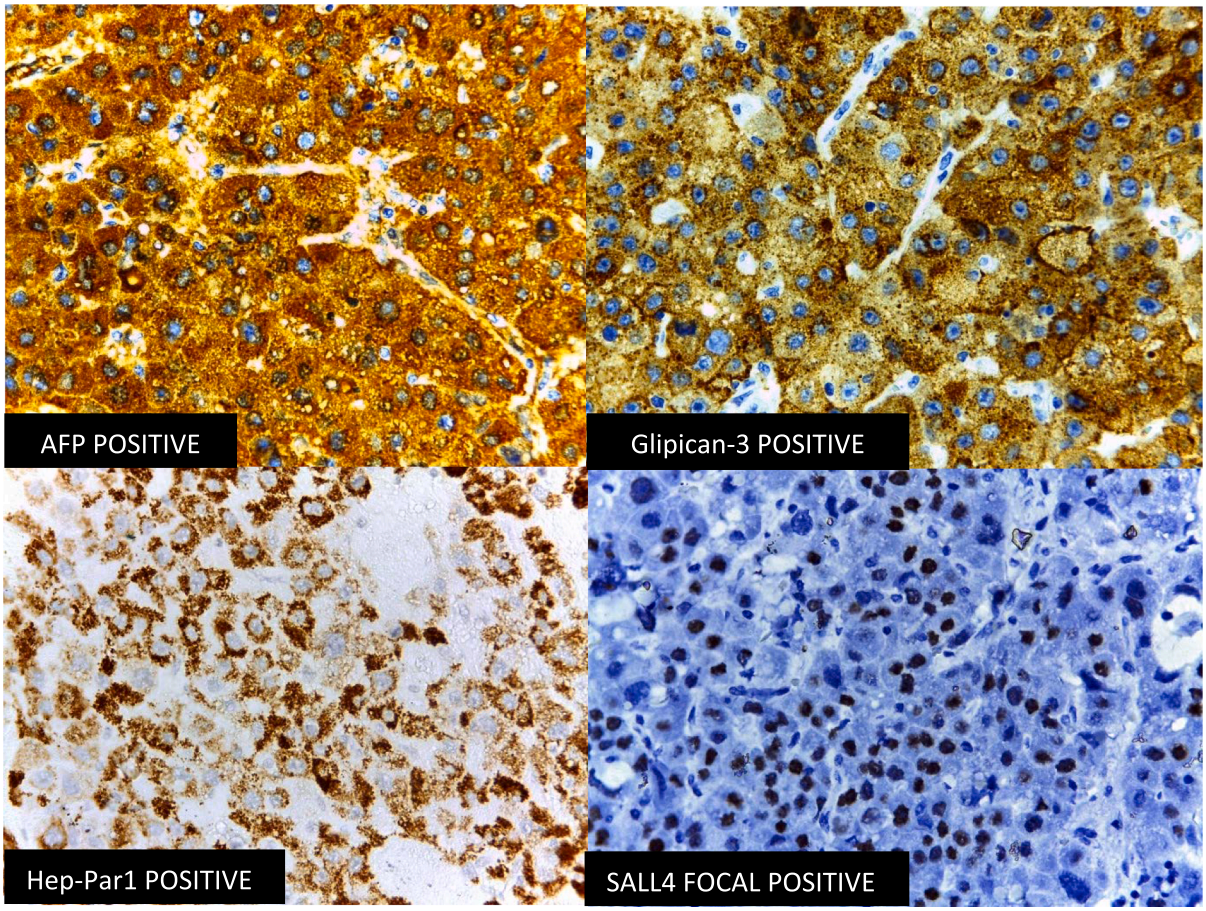

Fig. 1. Immunohistochemical findings.

3. Discussion

The first report was in 1987, by Ishikura and Scully (1987), they discovered five cases of ovarian tumors with cytological and morphology characteristics similar to hepatocarcinoma (HCC) without liver commitment. Age of presentation is 35–78 years, over 90% of cases present elevated AFP and Ca 125 can be raised in 60% of cases (Acosta and Pins, 2019).

The diagnosis is mostly in advanced clinical stages (III–IV), < 20% of patients have confined disease, and of those cases more than a half progress (Acosta and Pins, 2019). Macroscopically are multinodular, solid tumors, occasionally with cystic component, size between 5 and 35 cm (mean: 12 cm), usually unilateral, but 22% of cases are bilateral (Acosta and Pins, 2019). The association with alpha-fetoprotein (AFP) is over 90%, however, 8% of cases are negative (Sung et al., 2013).

They have been described in various organs, most frequently at gastrointestinal tract (stomach) (Young et al., 1992), also in lungs, gallbladder, pancreas, bladder, kidney, ovaries and uterus. In the genital area, 75% of cases are present in ovary (Cascales Campos et al., 2013), the absence of lesions in the liver parenchyma supports their diagnosis, but the presence of liver and ovarian lesions simultaneously makes the diagnosis very difficult especially when hepatocellular carcinoma rarely metastasizes to the ovary (Young et al., 1992). The median survival is 12 months, between the first and second year is 83% and 53% respectively (Randolph et al., 2015).

Macroscopic general features are tumors with solid and cystic component with white to yellow cut surface; as well as it is common to find hemorrhage and necrosis. Histologic features are a diffuse, trabecular/sinusoidal pattern and nested growth, which often coexist. Also, it can show extracellular hyaline bodies. The cytological features are polygonal cells with moderate to abundant eosinophilic cytoplasm, with distinct cell borders and central round vesicular nuclei with moderate to marked cytologic atypia and some of them with ≥1 nucleoli. Intracytoplasmic hyaline bodies can be observed. Also, frequent mitoses, including atypical forms are observed (Nucci and Oliva, 2018). Inmunohistochemistry features are AFP, Hep-Par1, α-1-antitrypsin, glypican-3, albumin, ck7, ck19 and ck20 positive; while the Pan keratin and CK8 are focally positive; on the other hand, these tumors are negative for calretinin, inhibin, synaptophysin, estrogen receptor and progesterone receptor (Wang et al., 2009). Differential diagnoses are the yolk sac hepatoid tumors that are SALL4 positive, this marker is more sensitive than classical IHC markers, such as placental-like alkaline phosphatase (PLAP), AFP, or glypican3, and strongly stains more than 90% of tumor cells. Positive staining for glypican3, AFP, and PLAP is seen in 100%, 95%, and 66% of cases, which does not occur in hepatoid ovarian carcinoma (Rittiluechai et al., 2014). Another differential diagnosis are metastatic hepatocellular carcinomas that have a multinodular growth pattern; and Steroid cell tumors, which have androgenic manifestations and are smaller cells with vacuolated cytoplasm, positive for inhibin, calretinin, SF1, WT1 (Wang et al., 2009; Rittiluechai et al., 2014).

Thirty-eight cases have been reported, and is still insufficient data to determine optimal treatment of these patients, there is no standard, most patients are treated with surgery (maximum cytoreduction) and adjuvant chemotherapy.

The use of biological therapy extrapolated in relation to hepatocellular carcinoma, sustainable data having little use, since, despite having pathological similarity between HCC and HCO these are biologically different, HCO has clinical aspect in relation to epithelial tumor. In the study by Pandey and Truica (2011) reported the use of sorafenib,

Table 1
Clinical, laboratorial, pathological, immunohistochemical, treatment and outcomes of HCO.

Case	Age	Site/size (cm)	Stage	Afp ng/ml	Ca125 U/ml	Ich	Surgery	Resection	Post op. treatment	Dissease control	Outcome	Reference
1	42	L 6.4; R 5.4	IIB	NA	NA	AFP + /AAT + /ALB + /ACT +	TAH + BSO + AP	R0	Ch-RT	Relapse: 4 years - carcinomatosis	Died (5 years)	Ishikura and Scully (1987)
2	71	L 20	IIIC	NA	NA	AFP + /AAT + /ALB + /ACT +	PC + TAH + BSO- + AP + Om	R1	RT	Persistence: 3 months post op, parasigmoid tumor	Alive (2 years)	Ishikura and Scully (1987)
3	57	R 10.5	IIIC	NA	NA	AFP + /AAT + /ALB + /ACT +	TAH + BSO + Om- + PARASPLENIC RESECTION	R1	NA	Persistence: 3 months post op, lower abdomen tumor	Died (4 months)	Ishikura and Scully (1987)
4	78	NA	IIIC	2420 (post op)	NA	AFP + /AAT + /ALB + /ACT +	BSO + COLECTOM-Y + POm	R0	MFL	Persistence: 4 months post op, tumor in left lobe of the liver	Died (8 months)	Ishikura and Scully (1987)
5	68	R 10	III	NA	NA	AFP + /AAT + /ALB + /ACT +	BSO + COLECTOM-Y + POm	R1	Ch-RT	Relapse: months, lesions at pancreas, liver, stomach, small bowel, abdominal lymph nodes, and spleen.	Died (10 months)	Ishikura and Scully (1987)
6	64	R 18	IA	23,170	58	AFP +	R-SO	R0	IP- CDDP	No progression during follow up period	Alive (2 years)	Matsuta et al. (1991)
7	62	R 8.2	IA	2450	NA	NA	NA	NA	B/VLB/CDDP; CDDP/E; CTX/ MMC/5-FU	NA	Died (13 months)	Tamakoshi et al. (1993)
8	52	NA	III	2500	Elevated	NA	NA	NA	CBDP/CTX/CDDP	Relapse	Recurred (7 months)	Badreddine et al. (1993)
9	43	L 7; r 8	IIIC	74	158	CEA + /ALB + /EMA + / AFP +	BSO + ATH + Om- + RL	NA	CDDP/EPIDX/IFX	No progression during follow up period	Alive (2 years)	Nishida et al. (1995)
10	72	L 9.5; r 5.5	III	500 (postop)	802	AFP +	ATH + BSO + RIG-HT HEMICOLECT-OMY + IOm	R0	CBDP	Relapse: 5 months, clinical and biochemical	Recurred (6 months)	Scurry et al. (1996)
11	35	L 35	IIIA	358	NORMAL	AFP +	L-SO + OMENTAL BIOPSY + ATH + R-SO + IOm	R0	CTX/CDDP/CBDP/E, PCTXL	Relapse: 18 months, tumor at pelvis, lower abdomen, liver metastases	Recurred/died (18/ 22 months)	Maymon et al. (1998)
12	53	L 9; R 8	III	NA	250	NA	DS	NA	CDDP/CTX	Relapse	Alive (12 months)	Trivedi et al. (1998)
13	61	L 12	III	73,080	79.7	AFP + /CK7 + /AAT + / ACT +	ATH + L-SO + POm	R0	IP CDDP; CDDP/5-FU/E	Relapse: 5 months laboratorial, 7 months paraesplenic mass and intraperitoneal tumor	Died (20 months)	Senzaki et al. (1999)
14	64	R 23	IIIC	900	52.7	AFP +	ATH + BSO + BPL- + Om + SEGMENT-AL RESECTION OF SMALL BOWL	R0	CDDP/CTX; CDDP/ PCTXL/RT; CDDP/ PCTXL	Relapse: 18 months, lesion in the mid-line of the retroperitoneum. 2 years, paraaortic mass	Recurred/died (18/5 years)	Lee et al. (2002)

(*continued on next page*)

Table 1 (*continued*)

Case	Age	Site/size (cm)	Stage	Afp ng/ml	Ca125 U/ml	Ich	Surgery	Resection	Post op. treatment	Dissease control	Outcome	Reference
15	36	L 10	IIIC	NA	888	AFP + /CEA + /AAT +	ATH + BSO + BPL- + Pao NODE BIOPSY + Om	R0	NA	NA	NA	Watanabe et al. (2003)
16	69	L 12	IA	589.5	11	AFP + /CEA + /ALB +	L-SO	R0	Patient declined	NA	NA	Tochigi et al. (2003)
17	53	L 10	IIB	257,522	NORMAL	AFP + /CEA + /ALB +	NA	R0	CBDP/PCTXL	No progression during follow up period	Alive (13 months)	Tochigi et al. (2003)
18	76	L 16	IIB	24,000	NA	AFP + /CEA + /ALB +	ATH + BSO + PARTIAL COLECTOMY	R0	None	No progression during follow up period	Alive (4 years)	Tochigi et al. (2003)
19	57	R 13	NA	24,879	NA	NA	ATH + BSO + Om	NA	NA	No progression during follow up period	Alive (3 years)	Tsung and yang (2004)
20	63	R 16	IA	454	84.59	AFP + /CK7 + /CEA + / ACT +	ATH + BSO + POm	R0	CDDP/CTX	No progression during follow up period	Alive (7 months)	Yigit et al. (2006)
21	40	R 11	III	32,338	1297	AFP + /CK7/CK8/CK18	DS	Nd	ChT	No progression during follow up period	Alive (6 months)	Kwon et al. (2006)
22	42	R 17	IA	600 (postop)	ND	AFP + /AAT +	ATH + BSO + BPL- + AP + IOm	R0	CBDP/PCTXL	Relapse: 6 months, pulmonary metastatic tumor	Died (16 months)	Lazaro et al. (2007)
23	50	L 10; R 8	IIIC	1.7	538	AFP + /CK + /EMA + /CK-7 +	ATH + BSO + Om- + Tumor excision from the pelvis and ileostomy	R2	CDDP/PCTXL; CDDP/GMZ; DXR	Progress	Died (2 years)	Ozan et al. (2008)
24	65	R 12	III	329,732	401.9	NA	ATH + BSO + Om	R1	CDDP/PCTXL	No progression during follow up period	NA	Gonzalez et al. (2008)
25	42	L 11	ND	ND	70	NA	ATH + BSO + Om	R0	NA	NA	NA	Zizi-Sermpetzoglou et al. (2009)
26	59	L 18	III	73,687	1599	AFP + /CK + /CEA +	ATH + BSO + POm- + Low anterior resection of rectum	R0	BEP	NA	NA	Isonishi et al. (2009)
27	34	R 14	IIA	NORMAL	NORMAL	NA	DS	NA	ChT	NA	NA	Sun et al. (2009)
28	42	L 6	I	NA	NA	AFP + /CK7 + /HEP PAR1 + /AAT + /CEA-/ INH-/CALRET-/ER-/PR -	L-SO/ATH + R-SO + AP + Om	R0	Ch-RT following recurrence	Relapse: 2008, alive at follow up with local progression	NA	D'antonio et al. (2010)
29	46	L 4.5; R 6.5	III	greater than30,000	414	CD99 + /INH + /CALRET + /HepPar1-/ AFP-/EMA-	ATH + BSO + Om- + BPL + DAF	R1	CBP/PCTXL-SORAFENIB	Relapse: 1 month, retroperitoneal and pelvic lymphadenopathy	NA	Pandey and Truica (2011)
30	55	L 11	IIIC	248.84	168	AFP + /HepPar1 + /INH-/ CALRET-/S100-/ SYNAPTO-	ATH + BSO + Om- + DAF	R1	IP nitrogen mustard; DCTXL/ NEDAPLATIN	Persistence abdominal disease	Alive (10 months)	Liu et al. (2012)
31	53	L 7; R9	IIIC	397	1247	AFP + (FOCAL)/CK7 + /INH + (FOCAL)/P53 + /CA125-/ PLAP-/HepPar 1-/CEA-/ EMA-	ATH + BSO + COm- + RDP + PP + AP	R0	HYPER ChT/CBP/ PCTXL- Relapse: RT	Relapse: metastasis in the L2 vertebra	Alive (28 months)	Campos et al. (2013)

(*continued on next page*)

Table 1 (*continued*)

Case	Age	Site/size (cm)	Stage	Afp ng/ml	Ca125 U/ml	Ich	Surgery	Resection	Post op. treatment	Dissease control	Outcome	Reference
32	57	NA 12	IIIC	761	124	AFP + /INH-/ER-/PR-/ PLAP-	BILATERAL ADNEXA DISSECT-ION + Om + DISSE-CTION OF METASTATIC NODULES ON THE MESENTERY + DAF	R0	CBP/PCTXL	No progression during follow up period.	Alive (15 months)	Wang et al. (2013)
33	51	R 9; l 8	IVB	2.2	37	AFP-/HepPar1-/ER-/ WT1-/P53 + /P16 +	ATH + BSO + AP- + TUMORECTOMY OF SIGMOID COLON	R2	1° line: CBP/PCTXL- 2° line: DCTXL	Progress: Left SC LP +, carcinomatosis, metastatic LN at retroperitoneum, bilateral iliac chain and retrocrural area. Abdominal mass, pleural effusion.	Died (6 months)	Sung et al. (2013)
34	73	L 24	IIIC	2396 (postop)	NA	AFP + /CK7 + / HepPar1 + (FOCAL)/SALL 4 + / ARGINASE + CALRET–	ATH + BSO + PAR-TIAL SMALL BOWEL RESECTION	R0	CBP/PCTXL	Progress: 7 weeks nodular mass in right upper quadrant, mass in the left side of the pelvis.	Alive (26 months)	Randolph et al. (2015)
35	78	R 9.9, L 4	IVB	150	100	AFP-/CK7-/HepPar1 + / INH-/CALRET-/S100 -/SYNAPTO-/EMA-	EXPLORATORY LAPAROSCOPY: PERITONEAL CARCINOMATOSIS	None	CBP/PCTXL	Progress: 1 month. Eight dorsal vertebra and pulmonar metastasic disease	Died (1 month)	Mazouz et al. (2015)
36	47	NA 10/ left lobe liver lesion 4	NA	6669	144	CK7 + /HepPar1 + / GLYPICAN +	LEFT PARTIAL HEPATECT-OMY + DS	R0	HIPEC: P	No progression during follow up period	Alive(22 months)	Naffouje et al. (2016)
37	47	R 10	NA	451	NA	AFP +	ATH + BSO	R0.Infiltr-ation of marrow, pancyto-penia.	ChT: NA	NA	Died (3 months)	Lakhotia et al. (2016)
38	41	L 5	IIIC	335	114	HepPar1 + /ARGINASE + /GLYPICAN 3 + /INH-/PAX8-/SALL 4-	CORE BIOPSY OF OMENTAL NODULE	R2. C.	Sorafenib. Progress: ChT CBP/PCTXL	Progress: 2 months	Died (2 months)	Mahmood et al. (2017)
39	27	R 10	IA	1210 (post op)	10.05	PANKERATIN + /AFP + /GLYPICAN + /HepPar 1 + /SALL-4 focal +	R-SO + PC + BPL + P-AoL + IOm + PB	R0	ChT: BEP	No progression during follow up period	Alive (3 years)	Present case

Abbreviations: IHC, immunohistochemistry; AAT, a1 antitrypsin; ACT, a1 antichymotrypsin; AFP, a-fetoprotein; ALB, albumin; CALRET, calretinin; Chromo, chromogranin; CK7, cytokeratin 7; EMA, epithelial membrane antigen; ER, estrogen receptor; HepPar1, hepatocyte-paraffin antigen 1; INH, inhibin; PAX 8, paired box gene 8; PR, progesterone receptor; SALL 4, Spalt-like transcription factor 4; WT1, Wilms tumor 1; RT, radiotherapy. C, carcinomatosisDS, Debulking surgery; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; R-SO, right salpingo-oophorectomy; L-SO: lenft salpingo-oophorectomy; Om, omentectomy; POm, partial omentectomy; COm, complete omentectomy; IOm, infracolic omentectomy; PC, peritoneal cytology; AP, appendectomy; RL, retroperitoneal lymphadenectomy; BPL, bilateral pelvic lymphadenectomy; PAoL, paraaortic lymphadenectomy; PB, peritoneum biopsies; RDP, right diaphragmatic peritonectomy; PP, pelvic peritonectomy; DAF, drainage of ascitic fluid; SC, supraclavicular; LN, lymph node; ChT: chemotherapy; CBP, carboplatin; PCTXL, paclitaxel; MFL, melphalan; EPIDX, epirrubicin, VLB, vinblastine; DCTXL, docetaxel; CDDP, cisplatin; BEP: bleomycin-etoposide-cisplatin; CDDP, cisplatin; CBDP, carboplatin; 5-FU, 5- fluorouracil; CTX, cyclophosphamide; GMZ, gemcitabine; DXR, doxorrubicine; MMc, mitomicine; IFX, ifosfamide; MMC, mitomicine; HIPER, hyperthermic intraoperative intraperitoneal chemotherapy; IP, intraperitoneal.NA, not available, R: right, L: left.

and showed no effects in these patients, other reviews mention progression-free survival of 7 months.

We have compiled the reported cases of HCO since 1987 to the present (Table 1), following the sequence performed by Randolph et al. (2015) and Acosta and Pins (2019), having 39 cases including our report. Of all these cases, our patient is the only one how comes out the usual scheme (age of presentation, laparoscopic conservation surgery and adjuvant treatment), she presented AFP 1210 ng/ml, following initial surgery was found in 10 ng/ml and after performing surgery and adjuvant chemotherapy AFP values have remained < 7 ng/ml. This case demonstrates that it is possible considerate conservation surgery in an early stage with good outcomes in relation to disease free survival.

4. Conclusions

Hepatoid carcinoma of the ovary is a rare neoplasm, highly aggressive, the most frequent presentation is in perimenopausal and postmenopausal age and usually the diagnosis it's in advanced disease. The treatment must be optimal cytoreductive surgery followed by chemotherapy. This is the first case reported in our institution and had conservative management. The clinical, imaging and laboratory evolution has been favorable with no evidence of disease relapse at 3 years follow-up.

Author contribution

This case report it's the first one presented in our country. Being an unusual pathology makes the treatment a challenge, and the presentation of this case is in age range it's uncommon.

However, radical surgery has been the standard treatment in the cases reported internationally, this is the first case report with different management with conservative surgery under laparoscopic guidance and the disease free survival until now it's 3 years.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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