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Review

Alpha-fetoprotein-producing non-germ cell tumours of the female genital tract

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ABSTRACT

Elevated levels of alpha-fetoprotein (AFP), a foetal serum protein, occur mainly on the development of hepatocellular carcinoma (HCC) or germ cell tumours, including yolk sac tumour (YST) and embryonal carcinoma of the ovary. Rarely, other tumours of the female genital tract produce AFP. This article reviews the AFP-producing non-germ cell tumours reported in different parts of the female genital tract to date. These include different types of carcinomas and carcinosarcomas of the uterus, ovary and cervix and sex cord stromal tumours of the ovary. It is important for both pathologists and oncologists to be aware of such cases and the clinicopathological distinction from germ cell tumours, as the diagnosis would affect the management plan for the patient. The reviewed cases suggest that regardless of the patient's age when no lesion is detected in the liver and stomach of a woman whose serum AFP level is abnormally high, the female reproductive system should be examined as a possible site of AFP-producing tumour. Biochemical, physiological and pathological features of AFP are briefly presented.

1. Introduction

Elevated levels of alpha-fetoprotein (AFP), a foetal serum protein, occur on the development of hepatocellular carcinoma (HCC) or germ cell tumours, including yolk sac tumour (YST) and embryonal carcinoma of the ovary. Hence, AFP is a useful tumour marker for germ cell tumours of the ovary and is valuable for both diagnosis and follow-up.[1]

There are non-germ cell tumours of the female genital tract that have been reported to produce AFP. These include different types of carcinomas, carcinosarcomas and sex cord stromal tumours. As the female genital tract is the site of germ cell tumours, it is important to be aware of other AFP-producing tumours, which should be considered in the differential diagnosis of tumours in patient with elevated serum AFP. This article reviews AFP-producing non-germ cell tumours reported in different parts of the female genital tract and discusses the distinction between these entities and YST.

2. AFP-producing non-germ cell tumours of the female genital tract

2.1. Ovary

2.1.1. Epithelial tumours

2.1.1.1. Hepatoid carcinoma. Hepatoid carcinoma, is a tumour that arises outside the liver but resembles, to a considerable extent, HCC both histologically and immunohistochemically in its staining for AFP.[2] The minimum histological criteria of hepatoid carcinomas are the evidence of AFP production and abundant eosinophilic cytoplasm.[3]

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Hepatoid carcinoma of the ovary has been reported in post-menopausal women presenting with unilateral or bilateral ovarian masses and elevated serum AFP. Microscopically, the tumour is characterised by solid sheets of large cells with abundant eosinophilic cytoplasm, central pleomorphic nuclei and distinct cellular borders. Tumour cells are diffusely immunoreactive for AFP and cytokeratin (CAM5.2).[3-6]

2.1.1.2. Ovarian serous carcinoma. AFP production has also been reported in primary ovarian serous tumours[7] and in one case AFP production was seen to develop following chemotherapy in an originally non-AFP-secreting ovarian serous carcinoma.[8]

One case was for a 66-year-old woman presenting with Cushing's syndrome. MRI showed a solid ovarian tumour and resection of the tumour led to normalisation of ACTH and cortisol levels. In addition, elevated serum vasopressin (ADH) and AFP were found, which were also normalised after removal of tumours. Pathological diagnosis was serous adenocarcinoma with neuroendocrine and hepatoid features. Immunohistochemistry detected immunoreactivity of chromogranin A, ACTH, ADH, and AFP in tumour cells.[9]

2.1.1.3. Ovarian clear cell carcinoma. AFP-producing clear cell carcinomas (CCC) of the ovary have been reported in post-menopausal women.[10] There are morphologic similarities between CCC of the ovary and YST, which can lead to a misdiagnosis of YST, especially when encountered in patients of young age. This issue is highlighted by a case report of a 17-year-old patient presenting with an ovarian mass, for which the diagnosis of YST was first suggested. However, because of non response to chemotherapy, a second laparotomy was performed and the definitive pathologic examination concluded the diagnosis of a CCC of the ovary. The young age and the immunohistochemical staining for AFP were unusual and misleading features for a CCC.[11]

In contrast to this case, Ballotta et al. reported a case of AFP-producing CCC in a post-menopausal woman. Morphologically the tumour showed features simulating the 'endometrioid-like variant' of YST. The tumour was characterised histologically by a villoglandular component intermingled with an endometrioid-like glandular pattern, nuclear pleomorphism with abnormal mitotic figures, eosinophilic hyaline PAS-D resistant bodies and diffuse, typical supranuclear and subnuclear vacuolisation. The age of the patient suggested the possibility of a surface epithelial tumour, which was substantiated by subsequent additional sections and immunohistochemistry.[12]

These two cases highlight the importance of being aware of the morphological overlap between different variants of YST and some epithelial tumours and the role and necessity of immunohistochemistry using the appropriate panel of antibodies to confirm the diagnosis.

2.1.1.4. Ovarian endometrioid carcinoma. A series of six cases of ovarian endometrioid carcinomas and one carciosarcoma admixed with typical YST component have been reported. The age of the patients ranged from 31 to 73 years. Immunohistochemically, the endometrioid areas differed from YST areas in their positivity for OC 125, CA19.9, nuclear estrogen and progesterone receptors and in their negativity for AFP, which was conspicuously positive in the YST areas. The ovarian endometrioid tumours with YST components occurred in the same age range as endometrioid carcinoma rather than that of YST. These tumours were managed as endometrioid carcinomas, but showed poor response to chemotherapy and aggressive behaviour.[13]

A case of AFP-producing pure ovarian endometrioid adenocarcinoma was reported in a 53-year-old woman. This was a predominantly well-differentiated endometrioid adenocarcinoma with small foci of clear cell components.[14] No germ cell component was detected in this tumour. Immunohistochemical analysis revealed that AFP was expressed in the cytoplasm of the endometrioid glandular lesions, but not in the clear cell components.

2.1.1.5. Ovarian undifferentiated carcinoma. Kuwashima et al. reported two cases of AFP-producing undifferentiated ovarian carcinomas.[15]

2.1.1.6. Ovarian mucinous carcinoma. A single case of ovarian mucinous cystadenocarcinoma-producing AFP was reported in a 62-year-old woman. Histologically, the tumour was a mucinous cystadenocarcinoma with a small area of solid proliferation of tumour cells, which were shown immunohistochemically to express AFP.[16]

2.1.1.7. Ovarian malignant mixed Müllerian tumour. A case was reported of a 52-year-old woman with an AFP-producing ovarian malignant mixed Müllerian tumour (MMMT). Immunohistochemistry confirmed that the carcinomatous component of this biphasic tumour was the seat of AFP production.[17] Nogales et al. also reported a case of carcinosarcoma with a yolk sac component.[14]

2.1.2. Sex cord stromal tumours

2.1.2.1. Sertoli-leydig cell tumour. The commonest AFP-producing non-germ cell tumour of the ovary is sertoli-leydig cell tumour (SLCT). To date there have been approximately 25 case reports of ovarian SLCT expressing AFP. Most of these tumours presented in young patients in the first three decades of life (17–18 years),[18–25] but also seen in post-menopausal women.[26]

Most of these sertoli-Leydig cell tumours were of the poorly differentiated type. In such cases, AFP was immunohistochemically detected in both Sertoli and Leydig cells, in Sertoli cells only,[20] in Leydig cells only,[27] or hepatocytic cells[28] and in one case AFP was detected in heterologous gastrointestinal epithelium.[25]

2.1.2.2. Granulosa cell tumour. A case of granulosa cell tumour of the ovary associated with raised serum AFP was reported in a 45-year-old patient. Histopathologically, the granulosa cell tumour was typically trabecular and the cells had nuclear grooves. Scattered diffusely throughout the tumour were small groups of regular polygonal cells, the cytoplasm of which was strongly positive for keratin, carcinoembryonic antigen (CEA), alpha-1-antitrypsin (A1AT), and ferritin and moderately positive for fibrinogen and ceruloplasmin, confirming hepatocytic differentiation.[29]

We encountered a case of a 16-years-old girl who presented with an ovarian mass and elevated serum AFP. Such presentation in a patient of young age raised the clinical diagnosis of germ cell tumour. Histological examination revealed a tumour with features of anaplastic juvenile granulosa cell tumour. Scattered focally were cells showing hepatocytic differentiation as confirmed by morphology and immunohistochemistry, which showed a profile identical to that described in the case by Nogales et al.[29] The specimen was thoroughly sampled and no germ cell component was identified.

2.1.3. *Metastatic tumours to the ovary*

The ovaries are common sites of metastatic tumours. A large array of tumour types are known to metastasise to the ovaries and hence secondary tumours should always be considered in the diagnosis of ovarian neoplasms, even in AFP-producing tumours. Examples of these are AFP-producing gastric carcinoma[30] and HCC. Several cases of metastatic HCC have been reported in the literature. De Groot et al. reported a case of a 47-year-old woman with a mass in the lower abdomen, 2 years after orthotopic liver transplantation for HCC. The findings of tumour cells arranged in trabecular and papillary aggregates, and the presence of bile-pigment, along with the patient's history helped the diagnosis of metastatic HCC.[31]

In conclusion the above cases show that primary and secondary non-germ cell tumours must be considered in the differential diagnosis of ovarian tumours with elevated serum AFP levels. Apart from typical yolk sac tumours, ovarian tumours with elevated AFP are uncommon and the differential diagnosis needs to consider the hepatoid pattern of a yolk sac tumour, sex cord stromal tumours, metastatic HCC, hepatoid carcinoma, and other epithelial ovarian tumours.

2.2. *Fallopian tube*

A single case of tubal carcinoma producing AFP was reported. This was a hepatoid carcinoma reported in a 52-year-old woman who presented with elevated serum AFP. A left adnexal mass was discovered on examination. Hysterectomy and adnexectomy revealed a $3 \times 3 \times 4$-cm tumour in the fimbriae of the left tube. Histologically and immunohistochemically, the tumour was confirmed to be an AFP-producing hepatoid carcinoma arising in the fallopian tube.[32]

2.3. *Endometrium*

Upon review of the literature on primary endometrial AFP-producing neoplasms two categories with different histogenesis and biological behaviour are encountered the primary YST of the uterus in young patients (range, 24–49 years; mean, 34 years),[33] and the rare AFP-producing non-germ cell tumours, which are commonly high grade endometrial carcinomas in elderly patients (range, 55–69 years; mean, 63.7 years). About 12 cases of the latter category have been reported and include.

2.3.1. *Endometrioid carcinoma*

Two cases of endometrioid carcinoma with AFP-producing cells have been reported. One case was a poorly differentiated adenocarcinoma.[34] The other case was endometrioid carcinoma with a hepatoid component.[35]

2.3.2. *Endometrial serous carcinoma*

Only two AFP-producing serous papillary endometrial carcinomas have been reported. One case was of a 55-year-old Japanese woman,[36] and the second case was from a 44-year-old woman who presented with vaginal bleeding, pelvic mass, and widely disseminated disease at presentation.[37].

We reported the third case of a primary AFP-producing uterine serous papillary carcinoma (manuscript under review). The patient was a 71-year-old lady who presented with post-menopausal bleeding. Her tumour markers taken at presentation revealed grossly elevated AFP (94,340 ng/mL). Multiple large lymph nodes were noted, with diffuse omental thickening and small volume ascites. The histology on the endometrial and cervical biopsies showed the morphological and immunohistochemistry profile of serous carcinoma. The tumour cells strongly expressed AFP, confirming the uterine neoplasm was the source of elevated serum AFP.

Our case and the two previously reported cases showed aggressive behaviour with tumour spread to the abdominal cavity, liver, lungs,[6] and pelvis.[1]

2.3.3. *Endometrial MMMT*

Cases of uterine MMMT with AFP production are reported in post-menopausal women. Some cases contained a hepatoid component.[38–40]

2.3.4. *Endometrial hepatoid carcinoma*

Hepatoid carcinoma in the endometrium may be present in pure form or in association with other types of endometrial tumours.[41]

Toyoda et al. reported a case of AFP-producing endometrial carcinoma in a 60-year-old woman with raised serum AFP. Histologically, the uterine mass showed a poorly differentiated endometrial carcinoma. The tumour was composed of the main medullary carcinoma area with microcysts and admixed small areas of well-differentiated endometrioid adenocarcinoma, with smooth transition between the two. In both, the tumour cells had immunoreactivity to AFP, alpha-1-antitripsin, albumin, transferrin, carcinoembryonic antigen, CA19–9, and epithelial membrane antigen. Based on these findings, this uterine corpus tumour was regarded as hepatoid variant of endometrial carcinoma.[42]

Hoshida et al. also reported a tumour that had two histologic patterns: one was a well-differentiated endometrioid adenocarcinoma and the other consisted of nests of cells resembling hepatocytes. In the hepatoid areas, giant cells and mitotic figures were frequent. Tumour cells in both the hepatoid areas and the glandular areas were immunoreactive for AFP.[43]

In contrast, Takeuchi et al. reported a case where the endometrial tumour showed a mixture of major AFP-negative endometrioid adenocarcinoma and minor medullary proliferation of the AFP-positive hepatoid adenocarcinoma cells with eosinophilic cytoplasm and hyaline globules.[35]

A case of hepatoid carcinoma in an MMMT of the uterus was reported in a 63-year-old woman. Histologically, the tumour was composed of endometrioid adenocarcinoma,

neoplastic hepatoid cells, and sarcoma component including leiomyosarcoma and rhabdomyosarcoma.[40]

Another case showed a collision tumour involving a hepatoid carcinoma and carcinosarcoma.[39]

2.4. *Cervix*

Only two cases of AFP-producing cervical tumours have been reported. One case was a poorly differentiated adenosquamous carcinoma.[44] The other case was a poorly differentiated adenocarcinoma with a hepatoid component. The tumour cells showed strong and diffuse cytoplasmic immunoreactivity with AFP in both components.[2]

Kim et al. derived a cell line from an invasive non-keratinising squamous cell carcinoma of the uterine cervix in a 31-year-old patient (CUMC-6). The epithelial nature of the cultured CUMC-6 cells was confirmed by transmission electron microscopy, which demonstrated the presence of desmosomes and tonofilaments. Cultured CUMC-6 cells produced human chorionic gonadotropin beta-subunit (beta-HCG) and AFP.[45]

2.5. *Vagina and vulva*

Yolk sac tumours of the vulva[46,47] and YST and AFP-producing embryonal carcinoma of the vagina[48–54] have been reported, but no AFP-producing non-germ cell tumours have been reported in the vagina.

2.5.1. *The use of immunohistochemistry in the differential diagnosis of AFP-expressing tumours of the female genital tract*

It is important to be aware that YSTs may mimic EACs and CCCs and that distinction is important for the clinical management of patients with these tumours. YSTs have a variety of morphologic patterns, some of which can resemble either endometrioid adenocarcinoma (EAC) or CCC and the use of immunohistochemistry is important in making the distinction. AFP is positive in 80% of cases of YST, but it is usually only focal and thus is not always helpful in the diagnosis of YST. Pancytokeratin (CK) is expressed by all three tumours.

Cytokeratin 7 (CK7) is essentially negative in YST, although a few tumour cells (1–2%) may express CK7. In contrast, almost all EAC and CCCs show diffuse strong expression of CK7. Leu-M1 (CD15) may be focally and weakly expressed in YSTs (60%), EACs (67%), CCCs (91%). EMA is essentially negative in YSTs, but is expressed in EAC and CCC.

Hepatoid carcinoma of the ovary commonly contains a population of clear cells, which may lead to the misdiagnosis of YST or CCC.[6] Histologically, it is also difficult to distinguish hepatoid carcinoma from the hepatoid variant of YST. In such cases, demonstration of CD10, Hep Par 1, membraneous patterns of p-CEA and CK7 would be invaluable for characterising the tumour as hepatoid carcinoma.

Sex cord stromal tumours are usually morphologically distinct from YST, but poorly differentiated tumours may represent some difficulty, in which case immunohistochemistry is useful. WT1 is negative in all cases of YST and CCC, but is positive in serous ovarian carcinomas and sex cord stromal tumours. Sex cord stromal tumours express inhibin and calretenin, which are both negative in YST.

3. Biochemistry and biological role of AFP

AFP is a glycoprotein with considerable homology with albumin. The molecular weight is approximately 70 kDa. AFP is an oncofoetal antigen, which is normally produced during gestation by the foetal liver and yolk sac. AFP concentration is increased in the maternal circulation during pregnancy and is also markedly elevated in newborns with concentrations declining over the first year of life. Under normal circumstances, synthesis of this protein, the foetal equivalent of albumin, virtually ceases shortly after birth. However, the protein is synthesised in large amounts and becomes detectable in plasma in about 70% of patients with HCC, and to lesser degrees in certain other tumours and benign liver diseases. AFP concentration is high at birth declining steadily to adult concentration by 6 months to 1 year of age. AFP can be expressed in malignancy – most frequently HCC and germ cell cancers, some oesophageal and pancreatic carcinomas and also in some benign conditions, particularly those associated with liver damage and/or regeneration.[1]

It has been demonstrated that several mRNA isoforms are transcribed from the AFP gene. In rats, it was reported that exon V, exists between exons 7 and 8, and the mRNA isoform (termed AFP-V mRNA) is synthesised using exon V in humans. Two exons, VA and VB, were identified. Furthermore, 3 AFP mRNAs, the AFP-V1, -V2, and -V3 mRNA, were demonstrated to be expressed through alternative splicing. Expression of the AFP-V2 mRNA isoform and the wild-type mRNA was differentially regulated, implying that the AFP-V mRNA isoforms could be used in diagnosis and classification of HCC and ovarian carcinoma.[55]

A sensitive technique for lectin-affinity immunoelectrophoresis was applied to samples from 28 infants and children in order to distinguish the origin of elevated AFP in sera. With combined use of concanavalin A (Con A) and lentil agglutinin (LCH) binding tests, AFPs were classified into three subtypes: benign hepatic condition type, hepatocellular carcinoma type and yolk sac type. AFP was of hepatocellular carcinoma type in all 7 patients with hepatoblastoma, and of benign hepatic condition type in six of seven patients with elevated AFP due to conditions such as hepatitis, biliary atresia, and normal newborn. The differentiation between yolk sac and general hepatic AFPs was tested with the Con A binding test.[55] Results of lectin affinity chromatography indicated that AFP produced by YST was different from the AFP to be found in the liver.[20]

In another study, in order to differentiate yolk sac-type AFP from hepatic-type AFP, 5 YSTs and 6 HCCs were examined immunohistochemically by the peroxidase-antiperoxidase (PAP) method for AFP, and paradoxical concanavalin A (P-Con A) staining, which has been reported to detect glycoproteins. In all 5 YSTs, AFP was negative for P-Con A staining. On the other hand, AFP was strongly positive for the same staining in all six HCCs. A similar staining pattern for AFP was observed in human yolk sac endodermal cells and embryonal hepatocytes. Thus, it was clarified that yolk sac-type AFP was unable to bind with Con A, in contrast with hepatic-type AFP, on tissue sections.[56]

Keel et al.[57] have demonstrated mitogenic activity for AFP, using a primary monolayer culture system of porcine granulosa cells from small ovarian follicles. In this system AFP alone does not stimulate proliferation. However, when combined with epidermal growth factor (EGF) and insulin-like growth factor-I (IGF-I), AFP significantly enhanced growth factor-mediated proliferation 4.5-fold over that of medium controls. The effects of AFP were dose dependent. Also AFP dose-dependently significantly increased proliferation of porcine granulosa cells in response to platelet-derived growth factor (PDGF) and EGF. These results demonstrate that physiological levels of AFP, although not mitogenic alone, can significantly enhance the mitogenic activity of EGF plus IGF-I/PDGF and may function to modulate growth factor-mediated cell proliferation during development and neoplasia.[57,58]

The objective of this review was to discuss the AFP-producing non-germ cell tumours that can be encountered in the female genital tract. It is clear that in addition to germ cell tumours, different sites of the female genital tract can develop other types of AFP-producing tumours. It is very important for both pathologists and oncologists to be familiar with the existence of these tumours. As demonstrated above some tumours may be mixed and include a germ cell component, which highlights the importance of thorough sampling of tumours. However, there are also pure forms of AFP-producing non-germ cell tumours. These tumours would have a different chemotherapeutic regimen and different prognosis from germ cell tumours. Hence it is important to recognise them as such and plan the appropriate management accordingly. The review demonstrates that raised serum AFP is not pathognomonic of a germ cell tumour and does not warrant giving the patient a treatment regimen for germ cell tumour if such a component is not identified by histology. Serological results need to be interpreted in the context of the patient's age, clinical presentation and histological features of the lesion. The reviewed cases suggest that regardless of the patient's age when no lesion is detected in the liver and stomach of a woman whose serum AFP level is abnormally high, the female reproductive system should be examined as a possible site of AFP-producing tumour.

4. Conflict of interest statement

None declared.

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