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Leading article

The interpretation of image-guided core biopsies in gynaecological malignancies

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Introduction

In the setting of gynaecological malignancies, there are three main approaches to obtaining image-guided core biopsies (IGCB): core biopsy of the omentum or peritoneum, transvaginal biopsies, and targeted biopsies. The most common and most accessible is the omentum or peritoneum when there is the presence of a large "omental cake" (Figure 1). On occasion, the omental route is not feasible to access the neoplasm seen on imaging. Ovarian masses present may however be accessible by the transvaginal route. Targeted biopsies may be required to establish the nature of metastases, such as in cervical lymph nodes where gynaecological malignancies may metastasize and may be one of the differential diagnoses.

There are three main clinico-radiological indications to perform IGCB in women who present with a clinical and radiological picture of disseminated peritoneal carcinomatosis suggestive of ovarian carcinomatosis.

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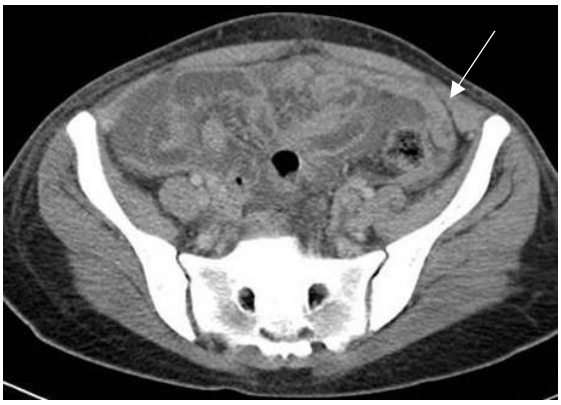

Figure 1: Image showing an "omental cake"

1) An ill patient who is unfit for primary cytoreductive surgery, but where it is imperative to get the correct diagnosis prior to commencing chemotherapy, so that appropriate neoadjuvant chemotherapy can be administered.
2) A patient who presents with a clinical picture of disseminated carcinomatosis where the tumour mimics an ovarian carcinoma e.g., a primary gastrointestinal (GI) malignancy which may be either upper or lower GI in origin, a breast cancer recurrence or even on rare occasions, metastatic malignant melanoma.

3) When the diagnosis is uncertain e.g., unusual imaging patterns of disease such as peritoneal carcinomatosis with bilateral solid ovarian masses, non-enlarged ovaries, or an unusual tumour marker profile, where tumour markers and radiology are not helpful in establishing a primary site of origin for the disseminated malignancy.

Most ovarian malignancies present at an advanced stage (stage III/IV). However, a minority will be confined to the ovary. These neoplasms will need distinguishing from other complex adnexal masses which may be benign. Either an ultrasound scan (USS) or magnetic resonance imaging (MRI) should enable their distinction. A biopsy of the mass following multidisciplinary team review will enable the correct diagnosis to be made in most cases so that appropriate management may be undertaken.

If the only available solid target lies deep in the pelvis and the percutaneous route is not feasible and the patient is unfit for surgery or an open biopsy, then a trans-vaginal biopsy may be another option available to obtain a core biopsy. This was first described in 1991 and 1992 (1,2).

An IGCB examination, with the confirmation by adjuvant immunohistochemistry and BRCA and homologous recombination deficiency (HRD) testing enables an accurate diagnosis to be made prior to neoadjuvant chemotherapy. This may then be followed by interval de-bulking surgery.

IGCB is performed by radiologists. It is a safe procedure and is well tolerated by patients. It has a high diagnostic accuracy, providing a site-specific diagnosis in 93% of cases (3).

Pathology of IGCBs

Irrespective of the method of obtaining the core biopsies, they are formalin fixed, paraffin embedded and then cut at 3–4-micron thickness. They are then stained with haematoxylin and eosin (H and E) and assessed for adequacy. These biopsies are usually turned around in 24 to 48 hours. If there is insufficient tumour on the initial sections, then further levels are undertaken. The preservation of morphology enables the tumour to be typed and graded on H and E sections, and adjuvant immunohistochemistry, when required, enables confirmation of the diagnoses in problematic cases (Figure 2).

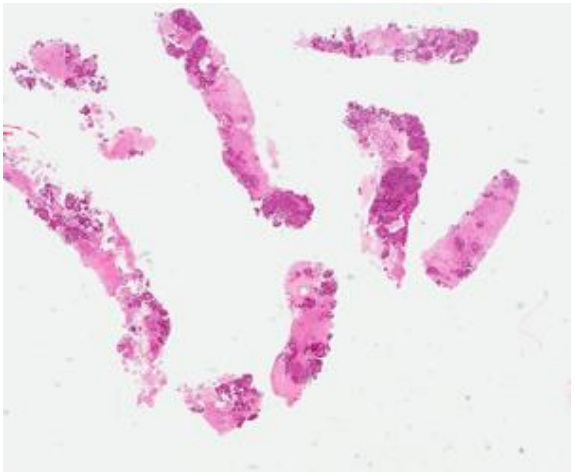

Figure 2: Omental core biopsies (H&E x40)

High-grade serous carcinoma (HG-SC)

The most frequent diagnosis made on the IGCB is that of a HG-SC irrespective of the route of obtaining the biopsy. The tumour may be characterized by solid sheets and papillary processes with intervening “slit-like” glandular lumina or exhibit a transitional-like morphology (Figure 3).

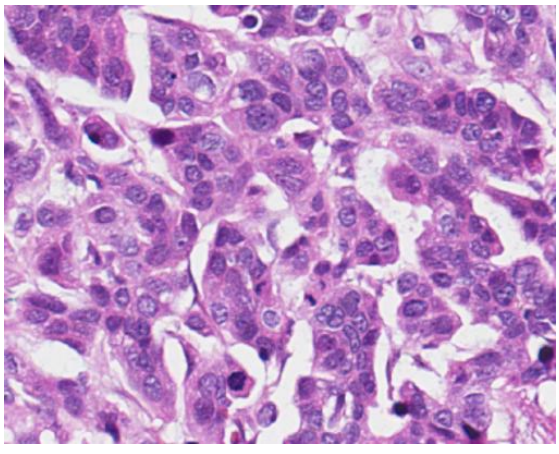

Figure 3: High-grade serous carcinoma (H&E x400)

There are however no clinically relevant morphological subcategories of HG-SC. Mitotic activity is frequent and atypical mitotic figures are commonly seen. Pleomorphic cells, with nuclei which appear as though they are smudged are not specific for HG-SC but are not uncommonly encountered. There is a marked variation in nuclear size and shape. The hyperchromatic nuclei have prominent nucleoli. Focal clear cell change may be encountered and should not lead the pathologist to diagnose a clear cell carcinoma. Immunohistochemistry (IHC) for hepatocyte nuclear factor-beta (HNF beta) or Napsin A would be helpful in excluding this diagnosis in doubtful cases (Figure 4).

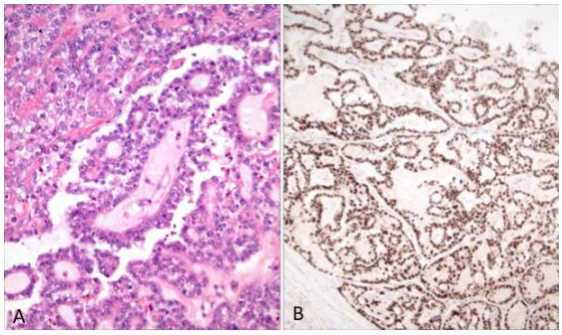

Figure 4: A Clear cell carcinoma (H&E x100)
B Clear cell carcinoma showing Napsin A positivity (IHC)

Targeted biopsies of an enlarged cervical lymph node may be performed. This is a case where a diagnosis of metastatic breast carcinoma within a supraclavicular lymph node was made and was followed by treatment for breast carcinoma (Figure 5A). Subsequently, 6 months later, an ovarian mass was identified with the diagnosis of a HG-SC on core biopsy. Upon review, the histology of the supraclavicular lymph node was found to be morphologically identical to the ovarian mass and was that of a HG-SC of tubo-ovarian origin (Figure 5B).

HG-SC may show two major types of mutational expression with p53. Either there is over expression in keeping with a mutation or "no reactivity pattern" suggestive of null-type of mutatinal pattern (Figures 6 A and B). A third pattern, which is rare, represents a cytoplasmic reactivity pattern which is also mutational. These tumours are WT1 positive. A negative WT1 pattern should prompt imaging to consider a primary tumour within the uterine cavity.

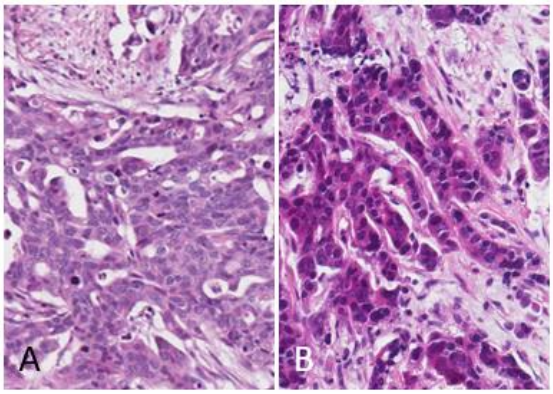

Figure 5: A Core biopsy of a lymph node with metastatic carcinoma (? breast carcinoma)
B IGCB of the ovary showing HG-SC (H&E x100)

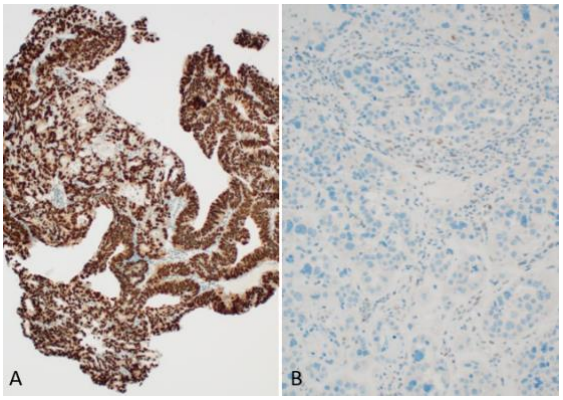

Figure 6: A p53 overexpression pattern (IHC)
B p53 null-type reactivity pattern with (IHC)

A panel of immunohistochemistry markers including p53, WT1 and ER and PR is helpful. The receptor status may be useful should hormonal treatment be a consideration at some time in the future. PAX8 can be added if there is concern that the lesion may not be primary müllerian in origin. GATA 3 together with ER may be helpful for breast tumour metastases and CDX2, CK7 and CK20 where metastases from the GI tract are a consideration.

HG-SC may be associated with a sarcomatous component (carcinosarcoma) but this component may not be seen in biopsy material

as the sarcomatous component does not always metastasize to the omentum. This is a pitfall in the diagnosis of carcinosarcoma on core biopsies. A poor response to chemotherapy may alert the multidisciplinary team to reconsider the diagnosis and this may lead to further imaging and re-biopsy/ definitive surgery to establish the diagnosis.

Solid, pseudo-endometrioid, and transitional cell carcinoma-like morphology (SET), which is characterised by a high mitotic rate, frequent bizarre mitoses and abundant tumour infiltrating lymphocytes is usually associated with germline or somatic BRCA-related abnormalities (Figure 7). Sometimes it may be seen in association with a combination of architectural features.

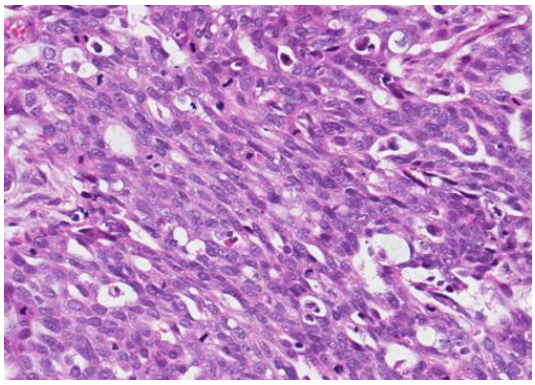

Figure 7: HG-SC with SET pattern (H&E x 200)

In a previous study that we did, comprising 149 patients, 75% of the women presented with disseminated ovarian carcinoma, however others had disseminated breast malignancies, gastrointestinal malignacy and lymphoma. There were two cases of benign mimcs of disseminated malignancy, tuberculosis and actinomycosis.

It was also interesting to note that when women with a diagnosis of breast cancer present with peritoneal carcinomatosis, they are more likely to have a new primary müllerian carcinoma than recurrent disease (4). This study was undertaken prior to routine BRCA testing of all patients with HG-SC.

Low-grade serous carcinomara (LG-SC)

The distinction of HG-SC from LG-SC, which is less frequent, relies on histoloigcal features. The cytology of HG-SC is characterised by hyperchromatic nuclei which vary in size (3 times or greater variation between nuclei) and the presence of tumour giant cells. The cells have prominent nucleoli. Mitoses are high (>12 per 10 HPF) and abnormal forms are frequent. LG-SC may be seen in association with borderline serous carcinoma, with a micropapillary pattern and numerous psammoma bodies (Figure 8A). LG-SC does not show p53 mutations as BRAF and KRAS are usually involved (Figure 8B). They are, however mutually exclusive. A Ki-67 may be helpful in establishing the low proliferation index. These tumours have a poor response to chemotherapy, therefore their histological distinction is important.

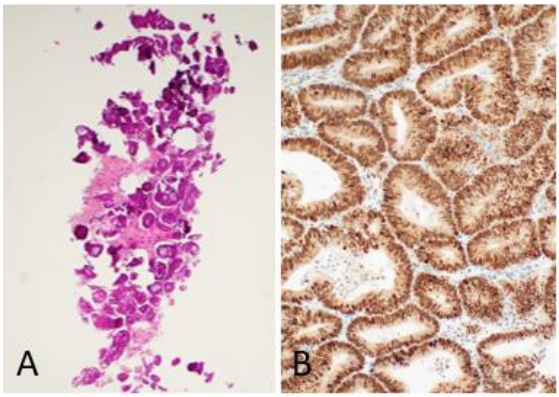

Figure 8: A LG-SC with psammomatous calcification (H& E x40) **B** Wild-type p53 mutation (IHC)

Endometrioid adenocarcinoma and mucinous carcinoma

Endometrioid adenocarcinoma is characterised by tall columnar cells with oval to pencillate nuclei lining rounded glands. The tumour architecture may be of tubular, cribriform, papillary or solid pattern. Squamous differentiation may be morular and mucinous differentiation may be seen. All these features may not be encountered in IGCB. Immunohistochemistry is usually negative for WT1 in contrast to HG-SC which would be positive. There is patchy positive reactivity for p16 in contrast to HG-SC which shows diffuse/ block positive reactivity. PR is diffusely positive, as is vimentin. P53 shows wild type reactivity in low-grade carcinoma,

however it may be mutant in high-grade endometrioid adenocarcinoma. PAX8 and nuclear beta-catenin are usually positive. If the differential diagnosis is with a bowel tumour metastasis CK20,CK7,CDX2 and SATB-2 can be added. In the distinction of mucinous carcinoma of ovarian origin from metastatic GI malignancy, there is a significant overlap and all these markers can be positive. There is no reliable marker at present to allow this distinction consistently. It is therefore imperative to use a panel of markers and the patient should be managed within the context of a multidisciplinary meeting with all the available clinical history. At times it might be necessary to perform either upper GI or lower GI endoscopy depending on the histological feautres of the tumour in the core biopsy to exclude a primary GI neoplasm.

Pseudomyxoma peritonei

Pseudomyxoma peritonei is a clinical diagnosis, describing an abdomen filled with mucinous material which may or may not include cells and in only certain cases malignant cells are present. Most cases arise from appendiceal mucinous neoplasms. Extra-appendiceal primary sites include: colon, pancreas, gall bladder, urachus or ovarian teratomas. Grading of pseudomyxoma peritonei is now recommneded by WHO 2020 tumour classification. The terms disseminated peritoneal adenomucinosis and peritoneal mucinous carcinoma have now been replaced (6).

Peritoneal mesothelioma

The presentation of peritonal mesothelioma is similar to ovarian carcinoma with vague symptoms comprising abdominal pain and distention, gastrointestinal disturbances, weight loss and ascities in most patients. Nodules and plaques involve visceral and parietal peritoneum. Most are epithelioid mesotheliomas with tubular, papillary and solid architecture or an admixture. Immunohistochemistry shows positive reactivity for calretinin, WT1, CK5/6 mesothelin, D2-40 and CK7. A small number are positive for PAX8 and therefore the importance of using a panel of markers cannot be over-emphasized. They are usually negative for Ber EP4, claudin-4, MOC31, B72.3, ER, PR, BAP1 and CD15. These markers are usually positive in carcinomas. Approximately half of the mesotheliomas show loss of nuclear BAP1 expression.

Metastatic carcinoma

Metastatic breast carcinoma may be encountered on occasion in omental core biopsies, they are not seen in transvaginal core biopsies where GI tumour metastases are more frequently seen (7).

Spindled cell neoplasms

Extragastrointestinal stromal tumours can involve the omentum, mesentery, and retroperitoneum. The neoplasm may represent metastases from an unrecognized primary or detached mass from the GI tract. It rarely involves solid organs e.g. the liver or pancreas. Histologically they are spindled, epithelioid, vacuolated, nested or myxoid. Approximately 70% harbour mutations of KIT or PDGFRA. Malignant melanoma must be considered, as in rare situations, it might present as a disseminated, spindled cell neoplasm. Immunohistochemistry for Melan A, S100 and SOX 10 as a panel would help establish the diagnosis.

Benign mimics

The potential mimics of ovarian carcinomatosis by benign conditions must not be forgotten. We have in our practice encountered two such issues; one was a case of tuberculosis and the other was actinomycosis.

Conclusion

An open mind is crucial in the interpretation of IGCB as they are small pieces of tissue which may not always be representative of the entire lesion. Close clinical and radiological correlation with the use of a panel of immunohistochemical markers is essential.

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