

CASE REPORT

Cancer of unknown origin in gynaecologic oncology

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Abstract

Tumour of unknown primary (primum ignotum) is a metastatic disease that generally shows a poor response to treatment and prognosis. Although it exhibits a trend of decreasing incidence, the diagnostic processes are complicated. The available literature shows that 5–30% of metastases involve the ovary, but it remains unclear how often ovarian infiltration is found in tumours of unknown primary. The most common metastatic disease that affects the ovaries are malignant tumours of the gastrointestinal tract, breast, pancreas, and haematological malignancies. Usually, the first step to distinguish between a primary and a secondary tumour of the ovary is an ultrasound examination, where the ovarian metastases have some characteristic features. Here we report our experience with primum ignotum in a patient with simultaneous ovarian and bone marrow involvement.

Keywords

Primum ignotum; Krukenberg tumour; Ovarian metastases

1. Introduction

Tumour of unknown primary—also called primum ignotum and cancer of unknown primary (CUP) is a metastatic disease. It comprises a heterogeneous group of tumours with aggressive biological and clinical behaviour, for which standard diagnostic algorithms do not lead to the identification of the disease origin [1, 2].

A cancer diagnosis is a complex process that includes a thorough history, clinical, laboratory, endoscopic, and histological examinations (immunohistochemical, molecular, and genetic analyses), and imaging methods. During the histological processing of a sample, the tumour is first classified into one of the main subgroups of tumours, and then its origin is identified. However, in cases of CUP, standard diagnostic procedures fail [3, 4]. Advancements in modern examination methods have led to a trend of decreasing occurrence of CUP, which now constitutes 1–5% of all malignant tumours [4, 5].

Two models have been proposed to explain CUP etiopathogenesis: the parallel progression model assumes that CUP arises from a clinically undetectable or regressed primary tumour, while the theory of the absence of a primary tumour considers CUP as a solitary entity that disseminates very early [3, 4]. A minority of CUP (15–20%) are histologically very similar to some known type of tumour, and these cases are chemosensitive and potentially curable [2, 6]. The most common CUP (70–80%) is metastatic adenocarcinoma of unknown origin (MACUP). Most CUPs are tumours that cannot be assigned to histological subtypes. They are poorly sensitive to chemotherapy and have a worse prognosis [2].

Due to the metastatic nature of the disease, systemic therapy is the primary treatment for CUP. Studies monitoring the

effects of different chemotherapy regimens (5-fluorouracil, doxorubicin, mitomycin-C, cisplatin, carboplatin, and others) have not demonstrated statistically significant differences in survival or recurrence [4, 6]. According to the European Society for Medical Oncology (ESMO), tumour-specific treatment is recommended for patients with a known histological subtype. If no histological subtype can be determined, the choice of therapy is influenced by the patient's overall condition [2]. In patients with a favourable prognosis (*i.e.*, in good overall condition and without elevated lactate dehydrogenase), the preferred treatment is combination chemotherapy with a platinum derivative and taxanes [2]. In patients with an unfavourable prognosis (performance status ≥ 2 and elevated lactate dehydrogenase), who would likely be unable to cope with aggressive systemic treatment, treatment is focused on preserving the quality of life; recommended treatment includes chemotherapy with low toxicity or symptomatic and supportive treatment [2, 4].

2. Case study

A 47-year-old female patient was sent to the gynaecology centre with the finding of a pelvic tumour, elevation of carcinoma antigen 125 (CA 125) 71.7 kU/L, and pancytopenia. The patient had no oncological history. She was being monitored for chronic anaemia and essential hypertension, and had overcome deep vein thrombosis of the lower limb and pulmonary embolism. She was currently a non-smoker, but until recently, had smoked about 15 cigarettes a day. At the first evaluation, the patient had no symptoms. There were no clinical manifestations of the anaemic syndrome, no pain, fever, night sweats, or weight loss. She had not experienced any other bleeding

besides long-term heavy periods and bruises.

Abdominal and vaginal ultrasound revealed regular multilocular-solid and solid ovarian lesions, bilaterally, up to 95 mm in size, with anechoic content. The tumours exhibited a smooth surface, and the number of locularities was about 5. Doppler showed very high perfusion (colour score 4). The solid component was homogeneous, and both lesions were mobile. There was no evidence of visceral or peritoneal carcinomatosis and no free fluid in the pelvis, but para-aortic lymphadenopathy was visible. The tumours were considered suspicious for malignancy and appeared to be metastases rather than a primary ovarian tumour (Fig. 1A).

The patient underwent colonoscopy, gastroscopy, thoracoscopy, and mammography, which showed no malignancy. The computed tomography (CT) scan findings were similar to those of ultrasound (Fig. 1B). Due to the pancytopenia and the high risk of bone marrow infiltration, the haematologist indicated a trepanobiopsy. Histology confirmed metastatic adenocarcinoma with reduced hemopoiesis. Haematological malignancy was excluded.

Next, the patient underwent exploratory laparotomy with removal of the ovarian tumours to provide sufficient material for histology and determination of the primary origin. A hysterectomy was not indicated due to the risk of bleeding and infectious complications. Perioperatively, bilateral smooth ovarian tumours were detected, which were freely mobile and non-adhesive (Fig. 1C). The pelvis and abdomen, including the peritoneum, were without pathology. The procedure was performed without complications, and with minimal blood loss, despite persistent profound thrombocytopenia.

The histological findings of both ovaries and tubes revealed metastatic adenocarcinoma with a signet ring appearance. The immunohistochemical profile showed positive results for *caudal-type homeobox transcription factor 2*, vimentin, mucin 1 and 5, cytokeratin 18, 20 and 7, and negative results for mucin 2 and 6, *paired box gene 8*, GATA binding protein 3, *thyroid transcription factor 1*, cyclin-dependent kinase inhibitor 2A (p16), estrogen and progesterone receptor, and napsin. The histological examination could not clearly define the tumour's origin, but it was decided to primarily focus on the gastrointestinal nature of the tumour.

Laboratory analyses revealed elevated serum levels of CA 125 (144 kU/L) and tissue polypeptide antigen (TPA-S) 346 U/L, and average levels of carcinoembryonic antigen, alpha-fetoprotein, cancer antigen 153 and squamous cell carcinoma antigen. The patient was experiencing bone pain and progressive shortness of breath during ordinary daily activities. In cooperation with the algologist, we adjusted the analgesic therapy, and the patient began rehabilitation. During hospitalisation, the patient was treated with numerous concentrates of irradiated de leukotized erythrocytes, platelets, and granulocyte colony-stimulating factors.

Due to the definitive exclusion of the gynaecological origin of the disease, the patient was transferred to a clinical oncologist's care with a diagnosis of metastatic adenocarcinoma—most likely Krukenberg's tumour from the stomach, with bilateral involvement of the ovaries and infiltration of the bone marrow. Systemic treatment with 5-fluorouracil was indicated. Severe back pain progressed, and a pelvis X-ray revealed

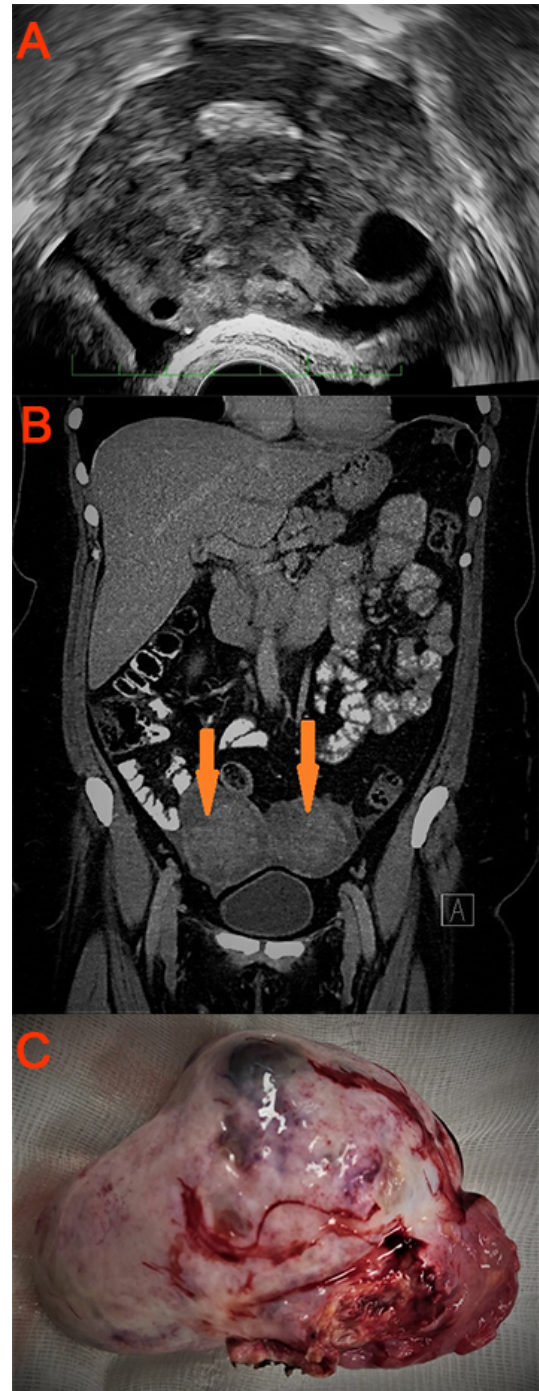


FIGURE 1. Ovarian malignant tumour of unknown origin. (A) The appearance of the ovarian secondary tumour on ultrasound. (B) Ovarian masses on CT scan—orange arrows. (C) Perioperative ovarian tumour exhibiting a smooth surface and high vascularity.

skeletal metastatic generalisation of the disease.

After the first cycle of palliative chemotherapy, the chemotherapy regimen was changed to oral capecitabine due to severe toxicity and sudden overall deterioration of the patient's condition. After three weeks, the oncology council terminated the oncological therapy due to further general worsening and profound pancytopenia (Fig. 2). The patient was transferred to the palliative care team for symptomatic and supportive treatment.

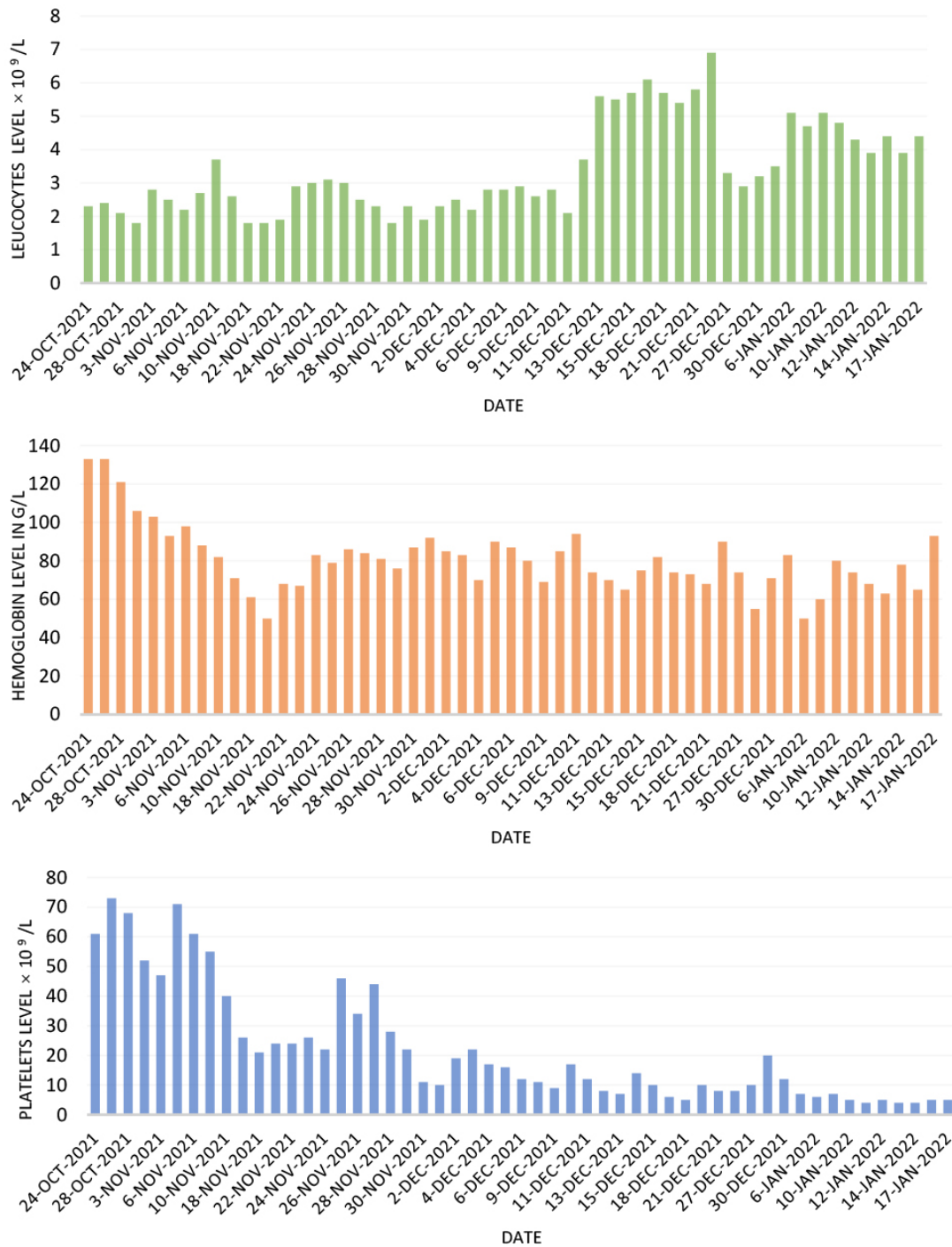


FIGURE 2. Hemoglobin, leucocyte, and platelet levels during diagnosis and treatment.

3. Discussion

A tumour of unknown primary is a metastatic disease constituting less than 5% of all malignant tumours. Although it remains unclear what percentage of these tumours affect the ovarian tissue, the ovaries are an easy target for metastatic processes thanks to their intensive hormonal activity, rich vascular supply, and lymphatic drainage [5]. The finding of a secondary malignant tumour of the ovary is not rare; 5–30% of all malignant tumours affect the ovary. Ovarian metastases of uterine, cervical, gastrointestinal, pancreas, breast, and haematological malignancies are common [4, 5, 7].

For the differential diagnosis of benign versus malignant ovarian tumours, an ultrasound examination is the first and often definitive choice. However, it can be difficult to distinguish between primary and secondary ovarian tumours, even with known specific ultrasound characteristics. On ultrasound, secondary ovarian tumours are mostly bilateral, solid or cystic-solid lesions, with regular contours, about 8–10 cm in size. Their vascularisation is of medium-to-high intensity, often with a characteristic single massive vessel (the so-called lead vessel) penetrating through the tumour hilum, with subsequent stromal tree-like branching. In a metastasis to the ovary, ascites occurs exceptionally, and diffuse or nodular peritoneal

carcinomatosis is rarely observed [7].

Histological diagnosis of metastatic involvement of the ovary is also challenging. A large sample volume is required to carry out a broad profile of immunohistochemical examination, followed by molecular and genetic tests [8, 9]. It is not guaranteed that sufficient material will be acquired in samples acquired using a tru-cut biopsy, a method often used in on gynecology. To obtain high-quality diagnostic material, it is recommended to avoid sampling the necrotic or haemorrhagic part of tumours, and suspicious lymph nodes. A direct ovarian tumour biopsy is preferred if accessible.

Among patients with CUP, treatment is better tolerated and has an improved prognosis when the patient is in generally good health. In MACUP with ovarian involvement, adnexectomy (metastectomy) improves prognosis and overall survival [9].

4. Conclusion

The occurrence of tumours of unknown origin shows a decreasing trend, thanks to advancements in modern examination methods. CUP diagnosis and treatment require a systematic approach and interdisciplinary cooperation, such that the centralisation of CUP patients to specialised oncology centres is inevitable.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

MR—data collection, wrote the manuscript. JK—data analysis, review and editing. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not require ethical approval because its ethical risk is minimal, and it is a case report. Written informed consent for publication was obtained from the patient.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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