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Case Study

# An Ominous Sign: Mucinous Ovarian Carcinoma with Sister Mary Joseph Nodule – a case report

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mOC, SMJN, gynaecology.

**Key Learning Points**

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1. The majority of women with ovarian malignancy present with advanced disease. This tendency for late presentation is mostly attributed to the vague nature of the associated symptoms – highlighting the diagnostic challenge ovarian cancer presents
2. Clinical examination in ovarian cancer requires vigilance for subtle signs to detect a pelvic mass or abdominal ascites. An umbilical 'Sister Mary Joseph' nodule (SMJN) may be easily overlooked, but provides a valuable clue to the diagnosis and is an ominous sign regarding prognosis.
3. Mucinous ovarian carcinoma (mOC) is a less common histological sub-type of ovarian cancer, more prevalent amongst younger women – contrasting with epithelial carcinomas, seen mostly amongst the post-menopausal population.
4. Our case report highlights the importance of optimal surgical effort to achieve R0 cytoreduction in cases of mOC, due to the low chemo-sensitivity of this tumour type.
5. We also discuss the challenge of embarking on pelvic clearance in women of child-bearing age who may not have had, or yet completed, their family – and hence the need for thorough and sensitive pre-operative patient counselling and ongoing support throughout.
6. This case also demonstrates the poor prognosis associated with anaplastic tumour components, which typically exhibit aggressive behaviour – with rapid disease progression and relapse.

**Abstract**

Despite two centuries of progress in its surgical and oncological management, ovarian cancer remains the most lethal of the gynaecological cancers, claiming the lives of nearly 185,000 women globally each year. Historically considered a single disease, there is growing recognition that ovarian cancer is in fact a spectrum of malignancies with distinct cellular origins, molecular driver pathways and clinicopathological features. Mucinous ovarian carcinoma (mOC) is a rare histological subtype that presents a particular challenge in accurate diagnosis and management. Frequently confused with metastatic deposits from extra-ovarian mucinous tumours, the true incidence of primary mOC is estimated to be between 3-5%. Typically affecting younger women, prognosis for late-stage disease is abysmal with a median survival of <15 months. This case report describes a 38-year-old patient who presented with rapidly worsening abdominal distension. Subsequent debulking surgery removed a mass weighing 2.4kg, confirmed
by histopathology as a high grade mucinous ovarian carcinoma with a mural nodule of anaplastic carcinoma. Evidence behind the current guidelines for management will be discussed, addressing our recent understanding of mOC as a separate disease from other histotypes and the consequent challenges in interpreting data from large multicentre trials in which patients with mOC are poorly represented. Moreover, using the Sister Mary Joseph nodule (SMJN) as an example, this case also highlights the importance of the physical examination and the value of subtle (and sometimes missed) clinical signs that provide important clues about the extent of a patient's underlying disease and prognosis.

## The Case

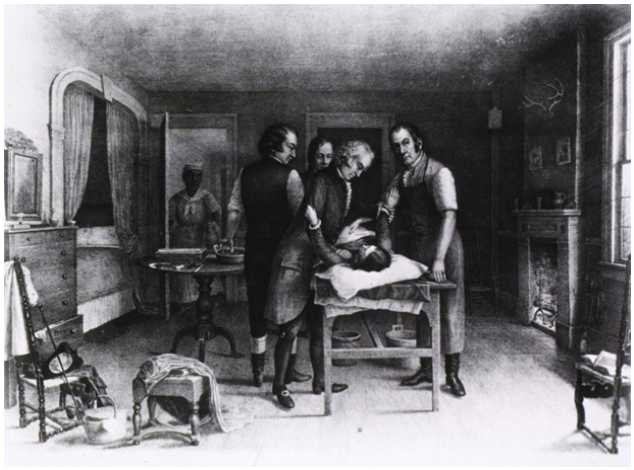
### Presenting complaint

EL is a 38 year old nulligravida who presented to her GP with a three-week history of painless abdominal distension and night sweats in July 2020. Abdominal examination revealed a fixed pelvic mass and diffuse abdominal ascites; urine pregnancy test was negative. Pelvic ultrasound showed an 18cm mass with solid and cystic components (Fig. 1), and EL was urgently referred to

the Gynaecology Oncology service on the 'red-flag' 2 week wait pathway. However, eight days before her scheduled appointment, EL presented to the Emergency Department with progressive dyspnoea, worsening abdominal distension, nausea, anorexia and severe lower back pain. She reported that the mass had doubled in size in the past week.

An environmental scientist by profession, EL has no significant past medical or surgical history and was in good health prior to the onset of her symptoms. Her only regular medication was hormonal contraception which she had stopped one month ago. A never smoker with no alcohol consumption, EL lives with her husband. There is no known family history of ovarian cancer or other malignancies.

On examination, EL was tachycardic (106 bpm) and febrile (37.8°C). The abdomen was soft but markedly distended with a palpable mass extending from the right iliac fossa (RIF) to the left iliac fossa (LIF), which was tender. Bowel sounds were present. Of note, a firm Sister Mary Joseph nodule measuring approximately 2.5 cm was palpable on the umbilicus. The nodule was nontender and the overlying skin was smooth with no ulceration. Examination of all other systems were unremarkable. Relevant blood results with tumour markers are shown in Box 1.



Ephraim McDowell performing (1809) the first ovariotomy, 19th-century lithograph. Image credit: National Library of Medicine.

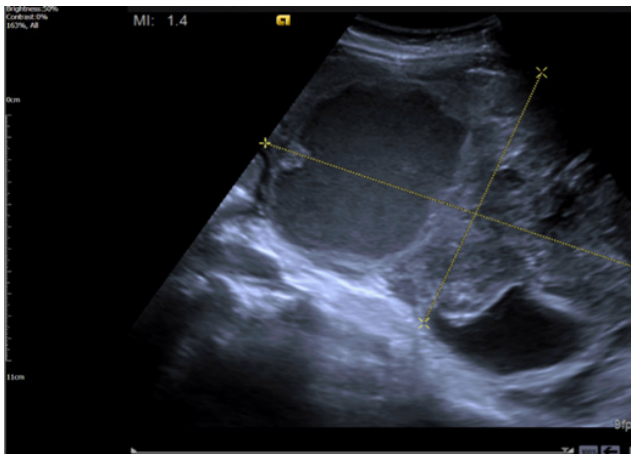



**Figure 1:** Transabdominal ultrasound sonography of patient EL. A left adnexal mass with solid and cystic components is shown, measuring 18.3 x 12.2 x 15.9cm.

| | | |
|---|---|---|
| Haemoglobin (Hb) | 111 | g/L |
| White cell count (WCC) | 14.7 | x 109 /L |
| Albumin | 20 | g/L |
| Cancer antigen 19-9 (Ca-19-9) | 1266 | U/ml |
| Cancer antigen 125 (Ca-125) | 419 | IU/ml |
| Carcinoembryonic antigen (CEA) | 2.0 | ug/L |
| α-fetoprotein (AFP) | <1.7 | IU/L |
| C reactive protein (CRP) | 244 | mg/L |
| Lactate dehydrogenase (LDH) | 365 | IU/L |
| Human chorionic gonadotrophin (hCG) | <1 | IU/L |

**Box 1: EL's blood results on admission with tumour markers. Values that exceed the normal range are red; those below the normal range are blue.**

**Investigations, diagnosis and pre-operative management**

EL was admitted and an urgent CT Chest Abdomen Pelvis confirmed a multiloculated 20cm mass arising from the left ovary (Fig. 2). The right ovary was radiologically normal. A solitary liver lesion was seen but later confirmed to be a benign haemangioma. The initial radiological staging was Stage IIIA primary ovarian cystadenocarcinoma. Histopathology from core needle biopsies indicated mucinous adenocarcinoma with a malignant mural nodule that could be sarcoma-like or anaplastic carcinoma.

A drain inserted in the RIF drained 7 litres of ascitic fluid, improving EL's breathlessness. However, she continued to experience severe lower back pain which worsened to the extent that EL was unable to lie down or sleep despite opiate analgesia via a patient-controlled analgesia (PCA) device. EL's preoperative management was further complicated by spontaneous bacterial peritonitis (SBP) following the ascitic tap and biopsy, resulting in a spike in the WCC (24.7 x 109/L) and CRP (316 mg/L). This was treated with IV co-amoxiclav.

EL's case was discussed by the Multi-Disciplinary Team and she was recommended for primary debulking surgery. The plan for surgery, which would start with an exploratory laparoscopy to assess tumour resectability, had three main potential outcomes, as shown in Fig. 3. EL was counselled on the possibility that if the disease was deemed unresectable at laparoscopy, it was inadvisable to proceed to a futile laparotomy with its associated risks of morbidity and mortality. On the other hand, if the tumour was resectable, depending on the degree of radical debulking required this could potentially involve bowel resection and formation of a stoma.

**Surgery**

EL was unable to tolerate lying supine for induction with general anaesthesia, requiring first a local block with epidural anaesthesia at the level of T8/9. During exploratory laparoscopy, pelvic and peritoneal disease was evident; there was no overt disease in the omentum, spleen, liver, falciform ligament or porta hepatis. The entire small bowel appeared suspicious for serosal disease, although the uniform appearance was more suggestive of post-SBP inflammatory fibrin deposits. Thus, the operation proceeded to primary debulking surgery with a midline laparotomy. The left ovarian mass was resected, measuring 230 x 160 x 160 mm and weighing 2.39 kilograms. The surface was irregular, and on sectioning, the cyst had a complex multiloculated appearance filled with thick mucoid

material. The surgery proceeded with bilateral salpingo-oophorectomy (BSO), total abdominal hysterectomy (TAH), en bloc pelvic and bladder peritonectomy, anterior colpotomy, total omentectomy, appendicectomy and bilateral pelvic lymphadenectomy. The surgery was complicated by intraoperative bleeding from a small laceration of liver segment 7/8 secondary to a friable and inflamed liver. The patient received 2 units packed red blood cells, 4 units fresh frozen plasma, 400ml 20% albumin and 3500ml of crystalloids. Haemostasis was achieved, with an estimated blood loss of approximately 1500ml.

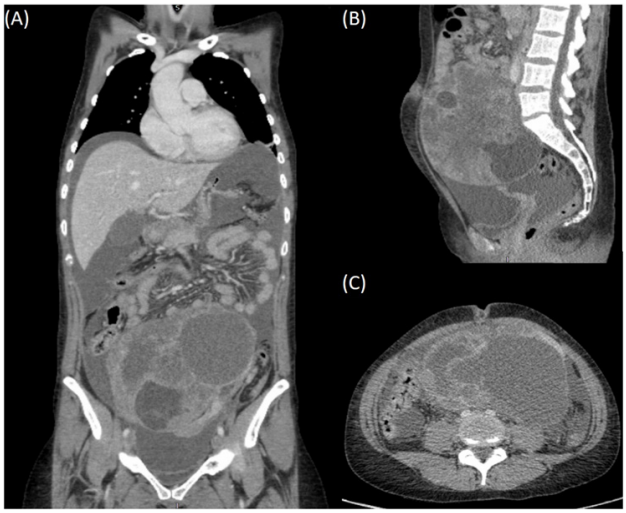



**Figure 2:** (A) Coronal CT image of the chest, abdomen and pelvis with IV contrast. A complex ovarian mass measuring approximately 20cm in diameter is visible. (B) Sagittal and (C) axial images show a hyperdense umbilical nodule measuring 2.5cm in diameter.

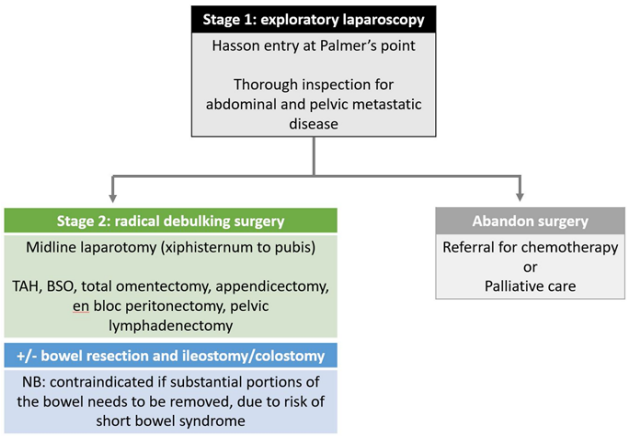



**Figure 3:** EL's operative plan, with three potential outcomes. TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy.

### Post-operative Recovery, Outcome and Follow up

EL recovered well from the operation and was discharged 12 days post-op.

The final histopathological diagnosis was high-grade primary ovarian mucinous adenocarcinoma and anaplastic carcinoma, FIGO stage IIIA2. The small bowel serosa was confirmed to show no tumour involvement. Complete surgical resection of the tumour was achieved and EL was referred for adjuvant chemotherapy. However, two weeks following discharge EL presented with severe acute kidney injury following 24 hours of anuria, requiring admission to ICU for haemodialysis. A repeat CT scan revealed bilateral ureteral obstruction and hydronephrosis, caused by a rapid and significant disease progression resulting in the retroperitoneal lymph nodes coalescing into a large mass. Pulmonary and hepatic metastatic deposits were also seen. Ureteral stents were inserted, but EL continued to deteriorate and passed away just over five weeks after the initial debulking surgery.

## Background

### What is mucinous ovarian carcinoma?

Each year, over 295,000 women worldwide are diagnosed with ovarian cancer with 185,000 associated deaths[1], making it the fourth most common cause of cancer death in females in the developed world[2]. Once considered a single clinical entity, there is increasing recognition that 'ovarian' cancer is in fact a spectrum of neoplasms with distinct cellular origins and clinicopathological features, which are reflected in their disease behaviours and outcomes[3] (Table 1). Epithelial ovarian cancer (eOC) is the predominant subtype (90% of cases) and is also the most lethal gynaecological cancer, characterised by late-stage presentation with a bulky metastatic disease burden. Indeed, a study examining US and UK registry data on 9491 women diagnosed with stage III/IV ovarian cancer found that 1 in 4 women died within the first 90 days of diagnosis, rising to 43% of women within the first year[4]. These stark figures are due in part to a lack of effective screening tools to detect pre-clinical disease at an early stage, combined with the relatively asymptomatic nature of eOC. When present, symptoms tend to be non-specific, including abdominal bloating and distension, nausea, early satiety and weight loss[5].

Mucinous ovarian carcinoma (mOC) is a rare histotype representing just 3-5% of eOC cases[6]. Compared to the more common High Grade Serous Ovarian Carcinoma (HGSOC), the age at diagnosis for mOC is much younger, with women under 44 years representing over a quarter of cases[7]. There is a dichotomy in outcomes: 80% of mOCs are diagnosed early at Stage I, according to the classification system of the International Federation of Gynecology and Obstetrics[8] (FIGO, see Table 2), conferring an excellent prognosis with 5-year overall survival of over 90%[9]. On the other hand, the minority of women who present with advanced or recurrent disease have an even poorer outcome than HGSOC, with an estimated median survival <15 months, compared to 41 months for serous histotypes[10]. One reason for this is the poor responsiveness to conventional platinum/taxane chemotherapy regimens. For such women, cytoreductive surgery plays a key role in their management to reduce the tumour burden as much as possible to maximise survival.

### Sister Mary Joseph nodule – a warning sign of advanced malignancy

In his textbook, Demonstration of Physical Signs in Clinical Surgery published in 1949, the British surgeon Sir Hamilton Bailey coined the term 'Sister Mary Joseph nodule' to describe a metastatic umbilical deposit from a primary abdominal or gynaecological malignancy[11]. The name acknowledged Sister Mary Joseph Dempsey, surgical assistant to William J. Mayo at St Mary's Hospital, Rochester (predecessor to the Mayo Clinic), who observed the association between the presence of a cutaneous umbilical nodule and subsequent discovery of underlying

intra-abdominal malignancy. To this day, the Sister Mary Joseph nodule (SMJN) remains the only eponymous clinical sign named after a nurse. When present, the SMJN is an ominous sign of advanced disease with a poor prognosis[12]. The umbilicus is an uncommon site of metastasis, and presentation can range from asymtomatic nodules to indurating painful ulcers Important differentials include primary umbilical pathology such as tumours and hernias. Although the mechanism is unknown, it has been postulated that convergence of embryonic remnants such as the ligamentum teres, along with a rich vascular and lymphatic supply, may create a route for metastasis to the umbilicus[13]. Identification of SMJN is important as it can sometimes be the first sign of abdominal or pelvic malignancy: in men it is typically associated with gastrointestinal cancers, but in women the most common cause is gynaecological cancer, particularly those of ovarian origin[14].

## Discussion

### Current guidelines for ovarian cancer management

In 2017 British Gynaecological Cancer Society published its latest guidelines on the management of ovarian cancer[15]. It recommends sequential testing with CA125 and pelvic ultrasound in women who present to primary care with suspicious symptoms such as abdominal distension and early satiety. If both tests are abnormal, or if a woman presents with an abdominal mass, urgent referral to secondary care is indicated. AFP and hCG levels should also be measured in women younger than 40 years to identify non-epithelial ovarian tumours. Once an ovarian tumour is presumed, radiological staging with CT abdomen chest pelvis is used to define the extent of disease and plan for any surgery. All patients with suspected or confirmed ovarian carcinoma are reviewed by the Multidisciplinary Team for the best management. Currently, radical upfront debulking surgery followed by adjuvant chemotherapy is considered the gold standard, although there is much debate in this area. In order to discuss the evidence base for the current recommendation for radical surgery, it is pertinent to first look back over time to appreciate how surgery for ovarian cancer has evolved.

### History of cytoreductive ovarian cancer surgery

Attempts at cytoreductive surgery for ovarian cancer has a history spanning over two centuries, beginning with the first successful resection of an ovarian tumour in 1809 by the American surgeon Ephraim McDowell[16]. A feat performed before the advent of anaesthesia or asepsis, McDowell was initially criticised for attempting surgery, yet by the end of the 19th century a new generation of surgeons emerged who, influenced by Rudolf Virchow's cell theory, embraced the idea that cancer in its initial localised stages could be amenable to curative surgery. Picking up the pace, the 20th century saw resection of metastatic ovarian cancers through proponents such as Meigs and Pemberton, culminating in the description of radical oophorectomy by Hudson in 1968[17]. But it was not until 1975, that Griffiths with his landmark paper conclusively demonstrated the inverse relationship between the size of residual tumour and survival in patients with stage II/III ovarian cancer, thereby providing quantitative evidence for the idea of 'maximum surgical effort' introduced by Munnell[18,19]. Critically, residual tumour volume of 1.5cm appeared to be the threshold; no improvement in overall survival was seen in patients whose disease could not be reduced below 1.5cm.

### Maximum surgical effort and 'optimal' debulking

Over the course of the 45 years that followed, the concept of 'optimal' cytoreduction has changed dramatically. In 2002, a retrospective meta-analysis including over 6800 women, Bristow demonstrated a 5.5% increase in median survival for each 10% increase in maximum cytoreduction, implying a need for ultra-radical surgery[20]. Since then, a steady stream of studies have confirmed a favourable link between smaller residual tumours and postoperative outcomes, from <1.5cm, then <1cm, to <0.5cm, and finally no residual disease (R0)[21]. This point is also emphasised in the current BGCS guidelines[15].

It should be noted, that while many studies have compared primary debulking surgery (PDS) versus neoadjuvant chemotherapy (NACT) with interval debulking surgery, this was not applicable in the case of EL and is beyond the scope of this case report (and word count).

### Primary, or metastatic? Challenges of diagnostic uncertainty

Over the last 15 years, our understanding of mOC as a unique disease entity has grown, bringing with it a number of challenges in its management and diagnosis. Firstly, the incidence of mOC is now considered to be substantially lower than previous estimates. In 2010, Zaino et al. published a retrospective analysis of pathology slides initially diagnosed as primary mOC, independently re-evaluated by expert pathologists[22]. Disturbingly, 50-70% of samples were found to be metastatic mucinous tumours of extra-ovarian origin, thus bringing the estimated incidence of primary mOC from ~12%[23] to between 3-5%[24]. The ovary is a frequent site of metastasis from mucinous tumours, especially from the colon, appendix and pancreas[25]. This finding has been replicated by further studies[26], calling into question whether results from classic literature on 'mucinous ovarian' carcinomas can be taken at face value, when most of the tumours were likely to have been misdiagnosed occult metastases.

Secondly, despite evidence from genomic studies that mOC is distinct from other subtypes not only in histology but also at the molecular level[6], patients still receive the same empirical treatment. In fact, 50% of mOCs harbour a KRAS mutation[27] and 20% have amplification of HER2[28], features not seen in other histotypes like HGSOC, in which loss of TP53 is the ubiquitous defect. Yet, current treatment guidelines reflect the conventional approach of treating all ovarian cancers as one disease, with the implication that patients may not be receiving optimal therapy tailored to their individual cancer subtype. For example, ICON7 was a phase III randomised controlled trial that evaluated the addition of bevacizumab to conventional carboplatin/paclitaxel[29]. Over 1500 women were enrolled, of which just 34 (2%) had the mucinous histotype, raising the concern that any difference in disease behaviour and response for these women could be lost due to averaging with other histotypes.

Finally, the rarity of mOC itself has been a challenge for attempts to conduct prospective phase II/III randomised trials specific to mOC. mEOC/GOG241 was one of the first international multicentre rare tumour trials on mOC. The aim was to compare the efficacy of capecitabine/oxaliplatin (a combination more commonly used in colorectal cancer) to conventional carboplatin/paclitaxel, with additional factorial randomisation to bevacizumab[26]. However, after 5 years it was terminated early due to poor patient accrual, having recruited just 50 patients out of a target of 322. Inadequate sample size is a common

| Histological subtype | Clinical findings | Genetic characteristics | Treatment options |
|---|---|---|---|
| High-grade serous carcinoma and high-grade endometrioid carcinoma | • Can present with peritoneal carcinomatosis, ascites and/or pelvic mass<br>• Typically advanced stage at presentation | • Deficiencies in homologous recombination (50% of tumours)<br>• Associated with *BRCA* and *TP53* mutations | • Platinum-based chemotherapy and poly(ADP-ribose) polymerase inhibitors<br>• Tumours are initially sensitive to platinum-based chemotherapy, but most patients with advanced-stage cancer will recur |
| Low-grade serous carcinoma | • Presents in younger patients (median reported age: 43–55 years[81])<br>• Can be early or late stage at presentation | • Associated with *KRAS* and *BRAF* mutations<br>• Tumours have genomic stability | • MEK inhibitors (currently being tested in clinical trials) and hormonal therapies |
| Low-grade endometrioid carcinoma | • Can be associated with endometriosis | • Associated with *PTEN*, *ARID1A* and *PIK3CA* mutations<br>• Can have microsatellite instability | • Possible hormonal therapies (not yet established) |
| Clear-cell carcinoma | • Can present with parenchymal metastases (in the liver and the lungs)<br>• Can be associated with hypercoagulability and hypercalcaemia | • Associated with *ARID1A* and *PIK3CA* mutations | • Immunotherapy agents<br>• Can be resistant to platinum-based chemotherapy |
| Mucinous carcinoma | • Presents in younger patients and is typically early stage at presentation | • Associated with *KRAS* mutations | • Tends to be insensitive to chemotherapy but is still treated initially with cytotoxic chemotherapy |

**Table 1:** Histological subtypes of epithelial ovarian cancer and their characteristics. Figure adapted from Matulonis et al. (2016)

| | |
|---|---|
| **Stage I.** Tumour confined to ovaries or fallopian tube(s) | |
| **T1-N0-M0** | IA: tumour limited to one ovary (capsule intact) or fallopian tube; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings<br>**T1a-N0-M0**<br>IB: tumour limited to both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings<br>**T1b-N0-M0**<br>IC: tumour limited to one or both ovaries or fallopian tubes, with any of the following:<br>IC1: surgical spill<br>**T1c1-N0-M0**<br>IC2: capsule ruptured before surgery or tumour on ovarian or fallopian tube surface<br>**T1c2-N0-M0**<br>IC3: malignant cells in the ascites or peritoneal washings<br>**T1c3-N0-M0** |
| **Stage II.** Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer | |
| **T2-N0-M0** | IIA: extension and/or implants on uterus and/or fallopian tubes and/or ovaries<br>**T2a-N0-M0**<br>IIB: extension to other pelvic intraperitoneal tissues<br>**T2b-N0-M0** |
| **Stage III.** Tumour involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes | |
| **T1/T2-N1-M0** | IIIA1: positive retroperitoneal lymph nodes only (cytologically or histologically proven):<br>IIIA1(i) Metastasis up to 10 mm in greatest dimension<br>IIIA1(ii) Metastasis more than 10 mm in greatest dimension<br>IIIA2: microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes<br>**T3a2-N0/N1-M0**<br>IIIB: macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes<br>**T3b-N0/N1-M0**<br>IIIC: macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)<br>**T3c-N0/N1-M0** |
| **Stage IV.** Distant metastasis excluding peritoneal metastases | |
| **Any T, any N, M1** | Stage IVA: pleural effusion with positive cytology<br>Stage IVB: parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity) |

**Table 2:** FIGO staging for cancer of the ovary, fallopian tube and peritoneal cancer. Corresponding TNM stages are shown. Adapted from the 2014 FIGO guidelines for staging classification by Prat et al. (2014)

problem with rare tumour trials; the difficulty in collecting sufficiently large datasets for statistical power, combined with lack of funding and research interest from industry which prioritises diseases with the greatest need/market, are just two of a number of factors which can hamper progress in finding innovative new treatments[30].

In summary, mOC is an uncommon disease affecting younger women. The case presented here followed a rapidly progressive course, and the presence of the SMJN served as an important sign on physical examination that was later confirmed by imaging and intraoperative findings. This report has summarised the unmet need in terms of optimal treatment for mOC. Further studies to identify disease at earlier stages are warranted.

## Conflicts of interest
None.


## Funding
None.


## Consent
The patient has consented to the publication of this case study.

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