

## CASE REPORT

# Cardiophrenic lymph node metastasis as the sole presentation of high grade serous ovarian carcinoma

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**Key Clinical Message**

Cardiophrenic metastasis is typically a late stage manifestation of ovarian high grade serous carcinoma. Here we present a case where this was the sole presentation of this disease. This case challenges our current understanding of the natural course of ovarian high grade serous carcinoma.

**Abstract**

Ovarian cancer is typically described to spread from its primary site within the fallopian tubes or ovaries into the peritoneal cavity and beyond with cardiophrenic lymph node involvement being considered a late stage disease process. Here we present the case of a lady in her 60s where increased metabolic activity of the cardiophrenic lymph node was picked up in the investigation of an adenocarcinoma of the lung. Post-thoracoscopic resection histopathological analysis of this lymph node showing an epithelial structure with positive immunohistochemical markers PAX8, WT1, ER, and p16 with a p53 wild type-pattern were the sole presenting features of a high grade serous ovarian carcinoma, that was otherwise undetectable by radiological or hematological screening. Only histopathological analysis after modified radical hysterectomy in gynae-oncological fashion were able to identify a 4 mm lesion within the left fallopian tube. This case questions our current understanding of the natural history of ovarian carcinomas.

**KEYWORDS**

cardiophrenic lymph node, FIGO, gynecological oncology, ovarian cancer, ovarian high grade serous carcinoma

## 1 | BACKGROUND

Ovarian cancer is considered the most fatal gynecological malignancy in the global health.<sup>1,2</sup> High grade serous carcinoma can have ovarian, tubal or peritoneal origin, with the latter being a rare presentation.<sup>3</sup> They are differentiated postoperatively by the degree of ovarian involvement and

microscopic cortical invasion.<sup>3</sup> Fifty percent to sixty percent of high grade serous carcinomas of the ovaries stem from the fallopian tubes. They are also referred to as serous tubal intra-epithelial carcinoma.<sup>3,4</sup> Within these, PAX8, which appears to also be associated in mucinous ovarian carcinoma,<sup>5</sup> and WT1 are common genetic markers of cancers with fallopian tube origin.<sup>6</sup> Staging, residual disease after

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primary surgery, and tumor type are the main factors influencing survival.<sup>3,7,8</sup> Preoperative computerized tomography (CT) scanning is the current standard for staging.<sup>9</sup> Due to poor screening and presentation with non-specific symptoms, ovarian cancer is usually diagnosed in its advanced stage (III–IV) in most patients when the tumor has spread throughout and beyond the abdominal cavity,<sup>2,10,11</sup> and often to the cardiophrenic lymph nodes.<sup>9,10,12,13</sup> However, while staged as IVb disease according to the International Federation of Gynecology and Obstetrics (FIGO),<sup>14</sup> it is unsure whether enlargement and invasion of the pericardiac lymph node reflects an advanced cancer stage or should be considered regional spread and therefore may not warrant labelling as stage IVb disease.<sup>12</sup> As advanced ovarian cancer should not be undertreated, therefore risking the patients' progression of disease, pericardiac lymph node involvement—even in the case of an isolated site—should be considered stage IVb and therefore treated by excision and chemotherapy. This should always occur in consultation of a multidisciplinary team (MDT) to carefully consider the different results of imaging, histopathological reports, and patient characteristics.<sup>11</sup>

In the majority of cases, due to their advanced stage, debulking surgery is the mainstay of treatment<sup>2,15</sup> and complete resection of all microscopically visible disease increases the chance of a good outcome.<sup>8,13,16</sup> This can be conducted via exploratory laparotomy or laparoscopy, and in advanced disease is used both for active treatment and to assess response to chemotherapy.<sup>7</sup> It aims at complete resection of all microscopically visible disease.<sup>8</sup> This operation is technically very challenging, especially when transperitoneal lymph nodes around major structures such as the porta hepatis are involved.<sup>2</sup> In the case of invasion of the thoracic cavity and enlarged cardiophrenic lymph nodes, surgical management can be achieved via transdiaphragmatic full thickness resection which facilitates access to the cardiophrenic lymph nodes.<sup>9,17–19</sup> This occurs in the following way described in<sup>18</sup>: “Following type 3 liver mobilisation, the diaphragm is stripped and muscle opened to gain access to the thoracic cavity. Transdiaphragmatic assessment of the cardiophrenic lymph node bundle is performed. A bulky node correlating with preoperative radiology is removed using an advanced energy device, maintaining the surrounding lung parenchyma and underlying pericardium safely in view throughout. The diaphragmatic is closed using a loop delayed absorbable suture and placing continuous, locking sutures.”

In stage IVb ovarian cancer, neoadjuvant chemotherapy with platinum based agents prior to interval or delayed debulking surgery is now state of the art to reduce disease activity of metastases on both sides of the diaphragm.<sup>2,5,8,13</sup>

## 2 | CASE HISTORY

We present this complex case of a lady in her late 60s and the development of her disease over 3.5 years. Initially, she presented to her GP with nausea increasing in frequency, persisting for some hours each day, weight loss, reduced energy, and changes in bowel habit.

Her past medical history includes anxiety and depression, psoriasis, coeliac disease, and a bladder prolapse. Her family history is positive for maternal ovarian cancer as well as breast cancer in a 2nd degree relative. She has a 30 packyear smoking history. As response to a major life event she had been prescribed venlafaxine (150 mg, once daily). She had stopped this abruptly in an indeterminate time period prior to her presentation.

She was referred to secondary care to investigate her symptoms as potential non-specific symptoms of cancer. Whilst her symptoms improved and she regained weight upon restarting venlafaxine, in the meantime she had undergone CT scan of her thorax, abdomen, and pelvis which showed several ground glass and sub-solid nodules in both upper lobes. These measured 17 mm with a 5 mm linear solid component and 13 mm with a 4 mm solid component in the left upper lobe. At 1 year follow-up investigation, one of the nodules in the left upper lobe had increased in size, from 17 to 23 mm with the 5 mm linear solid component having become more rounded and increased to 8 mm. This was suspected to be a T1b, N0 lung adenocarcinoma which was confirmed by CT guided biopsy; the left upper lobe of the lung was removed via video assisted thoracoscopy.

In subsequent postoperative CTs after 1 year, another spiculated nodule was identified in the right middle lobe which had increased by >1 mm in 1 year (from <5 to 7 mm). In the original CT screening scan this nodule had not warranted further investigation. Both the nodule and a cardiophrenic lymph node were avid by Herder on a positron emission tomography using a fluoro-deoxy-glucose radiotracer (PET FDG) suggesting malignant activity. The PET FDG also suggested that there was no avid distant disease. The patient underwent video assisted thoracoscopy Wedge resection of the right middle lobe and excision of the right diaphragmatic fat including the cardiophrenic lymph node.

Histopathological analysis of the primary tumor and the cardiophrenic lymph node both showed malignant activity but molecular analysis suggested two different origins of these malignant cells. The markers in the cardiophrenic lymph node were highly suggestive of gynecological high grade serous cancer of ovarian/tubal origin: The cells showed an epithelioid histology and were immunopositive for the markers PAX8, WT1, ER, and p16 with a p53 wild type-pattern, and

immunonegative for TTF1, Napsin A, PAX8, WT1, and p53 are known markers of gynecological cancers of fallopian tube origin.<sup>5,6</sup>

In appearance, it was described in the following:

“solid sheets and serpinginous nests and is composed of highly pleomorphic large nuclei that have a coarse chromatin pattern and striking nucleoli. Nuclei surrounded by moderate to generous volumes of cytoplasm. Mitotic figures including abnormal mitoses are frequent. There is a suggestion of focal cytoplasmic vacuolation, no clear squamous differentiation is seen.”

This was unlike those in the right middle lobe wedge where the histology displayed the structure of an adenocarcinoma with acinar architecture, the cells of which were immunopositive for TTF1, Napsin A and immunonegative for PAX8, WT1, ER, and p16.

### 3 | METHODS (INVESTIGATIONS AND TREATMENT)

Since the immunohistochemistry of the cardiophrenic lymph node was highly suggestive of a gynecological high grade serous carcinoma of the ovaries or fallopian tubes and could not be linked to the previous adenocarcinomas of the lung, blood tests, and imaging were used to investigate a potential gynecological malignancy.

Subsequent blood tests showed no evidence of this:

CA-125 20U/mL [ $<35$ ].

CA 19-9 8U/mL [ $<38$ ].

CEA 3.0ng/mL [ $<3.1$ ].

On a pelvic MRI and a further PET FDG of thorax, abdomen, and pelvis there was also no evidence of gynecological malignancy.

In the United Kingdom, gynecological cancer care is centralized and all relevant cases discussed in a MDT meeting typically consisting of gynae-oncological specialists, non-surgical oncologists and radiologists.<sup>20</sup> In a MDT meeting the consequences of having identified positive distant markers of a gynecological high grade serous cancer of ovarian/tubal origin despite blood and imaging evidence to the contrary of a primary tubo-ovarian malignancy were discussed. It was concluded that the lowest risk to the patient was to act upon the positive immunohistochemistry result suggestive of a high grade serous carcinoma, whereby cardiophrenic lymph node involvement is considered stage IVb disease according to FIGO.<sup>14</sup> In addition to the consequence of not acting on the positive immunohistochemistry result such as advancement of disease, two types of surgical approaches were discussed with the patient in accordance with the MDT: (1) A two step approach with initial bilateral salpingo-oophorectomy followed by hysterectomy on evidence of

tumor presence or (2) a modified radical hysterectomy in a gynae-oncological fashion (= laparoscopic omentectomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy). Since a high grade serous carcinoma may occur in both the ovaries and the fallopian tubes and due to the added uncertainty about the location of the tumor from prior negative imaging, it was deemed unfeasible to constrain surgical exploration to less invasive options.

In discussion with the patient it was decided that as the patient had completed her family and to avoid a second operation including general anesthesia, the most appropriate way forward for her was a modified radical hysterectomy in a gynae-oncological fashion to ensure complete resection of a potential tumor as well as metastases to the lymph nodes within the omentum which in the commonly accepted nature of the disease process would occur prior to cardiophrenic lymph node invasion.

During the surgery there was no macroscopic evidence of disease identifiable within abdomen, or the resected omentum (Figure 1) or the uterus, fallopian tubes or ovaries (Figure 2).

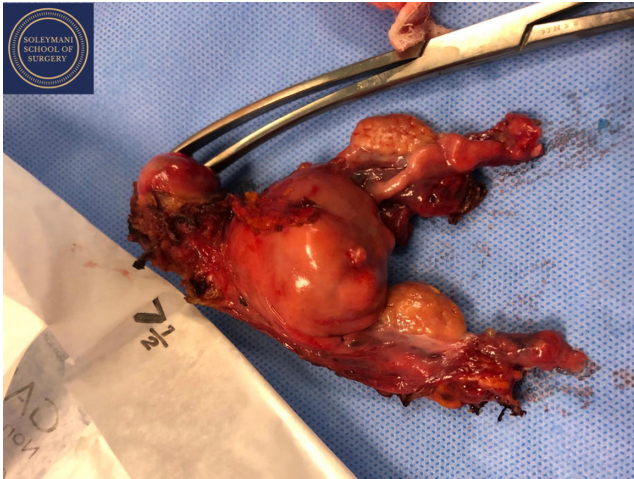
### 4 | CONCLUSION AND RESULTS (OUTCOME AND FOLLOW-UP)

Histopathological analysis of the resected tissue showed no macroscopic disease. Microscopic dissection subsequently demonstrated a high grade serous carcinoma of the fimbrial end of the left fallopian tube measuring 4mm in diameter with the molecular profile matching that of the cardiophrenic lymph node (positive markers: PAX8, WT1, ER, p16 positive with p53 wild-type pattern; negative markers: TTF1, Napsin A), without cancerous atypia within the structures of the ovaries,



FIGURE 1 Zouridis, (A) Resected Omentum (Photograph), Soleymani School of Surgery, unpublished.





**FIGURE 2** Zouridis, (A) Resected uterus, fallopian tubes, and ovaries (Photograph), Soleymani School of Surgery, unpublished.

the endometrium, myometrium, or omentum. This was proof that the abnormal cells within the cardiophrenic lymph node stemmed from a high grade serous carcinoma from the left fallopian tube, in absence of other metastatic disease.

She made a full recovery from surgery, and chemotherapy with carboplatin was initiated. She was followed up by the clinical oncological team and continued to receive CT investigations of her thorax, abdomen, and pelvis.

## 5 | DISCUSSION

This presentation challenges the commonly assumed natural course of high grade serous carcinoma of the ovaries/fallopian tubes.

It is described that ovarian cancer disseminates in the peritoneal cavity and eventually invades the thoracic cavity.<sup>21</sup> Most commonly this spread is to the cardiophrenic lymph nodes,<sup>9,10,12,13</sup> where the right side is most often implicated.<sup>21</sup> Here we are presented with a case that contradicts this assumption. This patient presented asymptotically with no preoperative hematological or radiological signs of gynecological disease. The only indicator of gynecological malignancy was positive identification of cells with positive immunohistochemistry PAX8, WT1, ER, and p16 on the histological sample of a metabolically active lymph node in the resection of a separate primary adenocarcinoma of the lung. The cardiophrenic lymph node was measured to be 7 mm which is on the low end of what is considered to be resectable disease. A node larger than 5 mm is defined as signaling metastatic disease by the European Society of Urogenital Radiology<sup>22</sup>; other studies suggest that only at >7 mm imaging has a

substantial (80%) chance of detecting metastatic activity.<sup>13,21</sup> However, involvement of the cardiac lymph node in the present case was the only site of disease metastasis; indeed it was the only primary indicator of disease activity prior to histopathological dissection of the tissue removed at surgery, which identified the primary tumor. There was no macroscopic pathology identifiable at surgery and histopathological analysis identified a primary lesion which measured 4 mm in diameter.

Cardiophrenic lymph nodes drain lymph from the diaphragm, the liver, pleura, pericardium, and anterior abdominal wall into the parasternal lymph nodes and the anterior mediastinal chain.<sup>12</sup> Due to their distribution and contribution to lymphatic drainage of the peritoneal cavity, it is pathophysiologically sensible to assume that invasion of the peritoneal cavity is the main cause of infiltration of the cardiophrenic lymph nodes.<sup>12,21</sup> While there are reports of isolated distal lymph node recurrences of high grade serous carcinoma<sup>23,24</sup> and cases where rare thoracic disease masquerades as ovarian malignancy,<sup>25</sup> to our knowledge it has not been reported before that a cardiophrenic lymph node can be the sole presenting feature of such a cancer. The literature reflects that involvement of the cardiophrenic lymph nodes are associated with prior involvement of the peritoneum and should therefore be considered a late stage disease process.<sup>9,21,26,27</sup> Furthermore, cardiophrenic involvement on pre-treatment imaging is an indicator of stage IV cancer behavior and consequently associated with poorer outcome of patients.<sup>9,12,26</sup> There is only one case reported that is reflective but not identical to the one presented here<sup>24</sup>: describe the case of a lady with a history of high grade serous carcinoma where in the presence of lung adenocarcinoma, there was recurrence isolated to the pleura and the cardiophrenic lymph node. Whilst<sup>24</sup> may hint at conclusions that can be drawn below, in the case we present, there was no prior known or detectable disease present.

The case as we report it here brings these reports and a classification of stage IV disease into question and the following hypotheses could be drawn from such a case:

1. Cardiophrenic lymph node involvement is only found in high grade cases as most cases are detected at late stages. Its association with poorer outcomes is statistical due to detection error.
2. Cardiophrenic lymph node involvement occurs as one of the first presentations in high grade serous carcinomas that will go on to develop into transperitoneal disease
3. Malignancy or other co-morbid factors of a patient may influence the course and spread of the disease process; malignancy in the thoracic cavity may have provided an apt seeding ground

4. This is a very uncommon presentation and should be considered an outlier in absence of further literature

At this point in time, this case report stands in opposition to many cases that have been described before; we therefore propose a rigorous investigation of the above hypotheses. At this point in time, primary staging remains paramount in identifying the primary lesion. The initial indication for the presentation of a gynecological malignancy was found on the background of a different malignant process and is therefore an unusual case in the diagnostic pathway. In the presence of an unusual presentation of disease we must involve the robust work of a MDT to think outside the box whilst going back to the primary understandings about a disease. Nonetheless it calls into question our current understanding of the so-called natural course of progression of high grade serous carcinomas of the ovaries and fallopian tubes. It further opens up questions regarding the follow-up our patient, for example, via monitoring circulating DNA which is promising to monitor tumors that are so far undetectable on imaging or common biomarkers.<sup>28</sup>

#### AUTHOR CONTRIBUTIONS

**Thomas Julius Henning:** Conceptualization; data curation; formal analysis; methodology. **Andreas Zouridis:** Conceptualization; data curation; investigation; methodology. **Hooman Soleymani Majd:** Conceptualization; data curation; investigation; methodology; project administration; resources; supervision; validation; visualization; writing – review and editing.

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#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.


#### ETHICS STATEMENT

This manuscript has not been published elsewhere.

#### CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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