

Primary peritoneal cancer presenting with widespread lymphadenopathy, radiologically mimicking lymphoma

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Summary

Primary peritoneal carcinoma (PPC) is a rare malignancy with clinical features and management similar to epithelial ovarian carcinoma (EOC). Lymph node involvement in EOC or PPC is commonly seen in the presence of advanced disease with peritoneal involvement and rarely a presenting symptom. We describe a rare case of PPC in a 74-year-old woman presenting with widespread lymphadenopathy, radiologically mimicking lymphoma without peritoneal involvement. To our knowledge this is the only case of PPC presenting with supraclavicular and widespread lymphadenopathy, in the absence of macroscopic disease. This case may represent a distinct clinical entity from the usual peritoneal dominant form of EOC or PPC and highlights important clinical and biological aspects of PPC.

Key words: Primary peritoneal carcinoma; Epithelial ovarian carcinoma; Lymphadenopathy.

Introduction

Primary peritoneal carcinoma (PPC) is a rare malignancy [1] that develops from the abdominal and pelvic peritoneum [2]. It accounts for approximately 10% of presumed diagnoses of ovarian cancer [2]. PPC typically presents with abdominal distension, pain and gastrointestinal disturbance [2] and is clinically similar to epithelial ovarian carcinoma (EOC), the main difference being lack of ovarian involvement in PPC [1]. The Gynaecology Group (GOG) has set criteria for the diagnosis of PPC: 1. Normal sized ovaries/enlarged by benign process 2. Involvement of extra-ovarian sites greater than of the surface of either ovary 3. Ovarian component must be a) non-existent b) confined within the surface epithelium or c) involve cortical stroma with tumour size less than 5×5 mm [1].

There are two theories on the pathogenesis of PPC [2]. The first is PPC develops from malignant transformation of embryonic germ cells along the gonadal embryonic pathway [2]. The second is the peritoneum and ovaries, which share a common embryological origin [3], undergo malignant transformation as a response to oncogenic stimuli [2]. Molecular studies have shown involvement of HER2/neu, p53, WT1, PR, ER [4], and PAX8 [5] in carcinogenesis of PPC [4, 5]. PPC commonly spreads transcoelomically within the peritoneal cavity, whereas EOC metastasises via the lymphatics, transcoelomically, and (2-3% of cases) haematogenously [6].

Management of PPC/EOC involves cytoreductive surgery and platinum-based chemotherapy [1]. The median survival times vary between 7.0 and 27.8 months [1].

PPC or EOC presenting with lymph node (LN) metastasis is uncommon and those presenting with lymphadenopathy invariably involve the ovary, peritoneum or omentum on staging. We present a case of PPC presenting with widespread lymphadenopa-

thy, radiologically mimicking lymphoma. We review the literature and discuss the possible underlying biological hypotheses for such a presentation.

Case Presentation

A 74-year-old lady presented with a 4-6-week history of enlarging mass in the left side of the neck. She had been well otherwise with no accompanying systemic symptoms. Her blood profile was within normal limits. Her performance status was zero. Her past medical history included mitral valve repair, hypertension and hypothyroidism. Her medications included Warfarin, Thyroxine, Felodipine, Losartan and Atorvastatin. Family history showed her father had lung cancer. She was a non-smoker and drank alcohol on social occasions.

Examination revealed mid-sternotomy scar, a large supraclavicular fossa mass measuring 4×5 cm and engorged veins with collaterals across the left chest wall. There was slight oedema of the left breast but no palpable masses in either breast and no other palpable lymphadenopathy. Computed Tomographic Scan (CT) showed cardiomegaly, left supraclavicular $2.8 \times 3.6 \times 4.6$ cm nodal mass compressing the left internal jugular and subclavian vein, further nodal deposits up to level five of the neck, retrocrural, portocaval and upper abdominal lymphadenopathy (Figure 1). There was no peritoneal/omental abnormality and no pelvic masses (Figure 1). Radiologically the findings were consistent with lymphoma.

Mammogram and Ultrasound scan of the left breast showed no malignant lesions or axillary lymphadenopathy. Biopsy of the LN showed disrupted LN extensively replaced by poorly differentiated carcinoma with extensive necrosis (Figure 2A). Immunohistochemistry revealed expression of AE1/3, CK7, CA125 (Figure 2B), ER (quick score 7) PAX8 (Figure 2C), p53, WT1, mesothe-



Figure 1. — Computed Tomographic Scan (Axial and coronal sections) showing a large left supraclavicular lymph node (green long arrow) and retroperitoneal lymphadenopathy (green and red arrow heads) with no peritoneal involvement.

lin, Ber-EP4 (focal). CK14 (focal), Cal9-9 (focal). It was negative for CK20, PR, GCDFP, TTF1, S100, p63, CK5/6, CSA, CDX2, synaptophysin or chromogranin. Ki67 index was $> 70\%$. Overall, the morphology and immunohistochemical profile was consistent with metastatic high-grade serous carcinoma of either ovarian or primary peritoneal origin.

Our case fitted with the diagnosis of PPC and met the GOG criteria for diagnosis, except we could not demonstrate the absence of microscopic involvement. Given the lack of macroscopic peritoneal/omental involvement and absence of pelvic masses, we did not proceed with cytoreductive surgery as this would not have altered the management plan, which was upfront systemic treatment with platinum-based chemotherapy.

She had a partial response after six cycles of Carboplatin and Paclitaxel. She was placed on maintenance aromatase inhibitor, Letrozole, after chemotherapy and she remained asymptomatic for a year with no clinical or radiological evidence of disease progression. Fourteen months after the completion of chemotherapy, she

became symptomatic and follow-up CT showed progression particularly in the intraabdominal lymphadenopathy. She was treated with six cycles of Carboplatin and achieved stable disease. However, three months after completion of Carboplatin, she developed symptomatic disease progression and her performance status was declining. We planned to treat her with weekly Paclitaxel but she deteriorated and died peacefully at home, thirty months after original presentation.

Discussion

To our knowledge, this is the only case of PPC presenting with supraclavicular and widespread lymphadenopathy without macroscopic disease in the peritoneum and pelvis, which is common with advanced EOC or PPC.

Literature review shows many case reports and case series of isolated nodal relapse as well as new ovarian cancers presenting with lymphadenopathy. In one series lymph node enlargement was one of the presenting symptoms or a surgical finding in 11% of

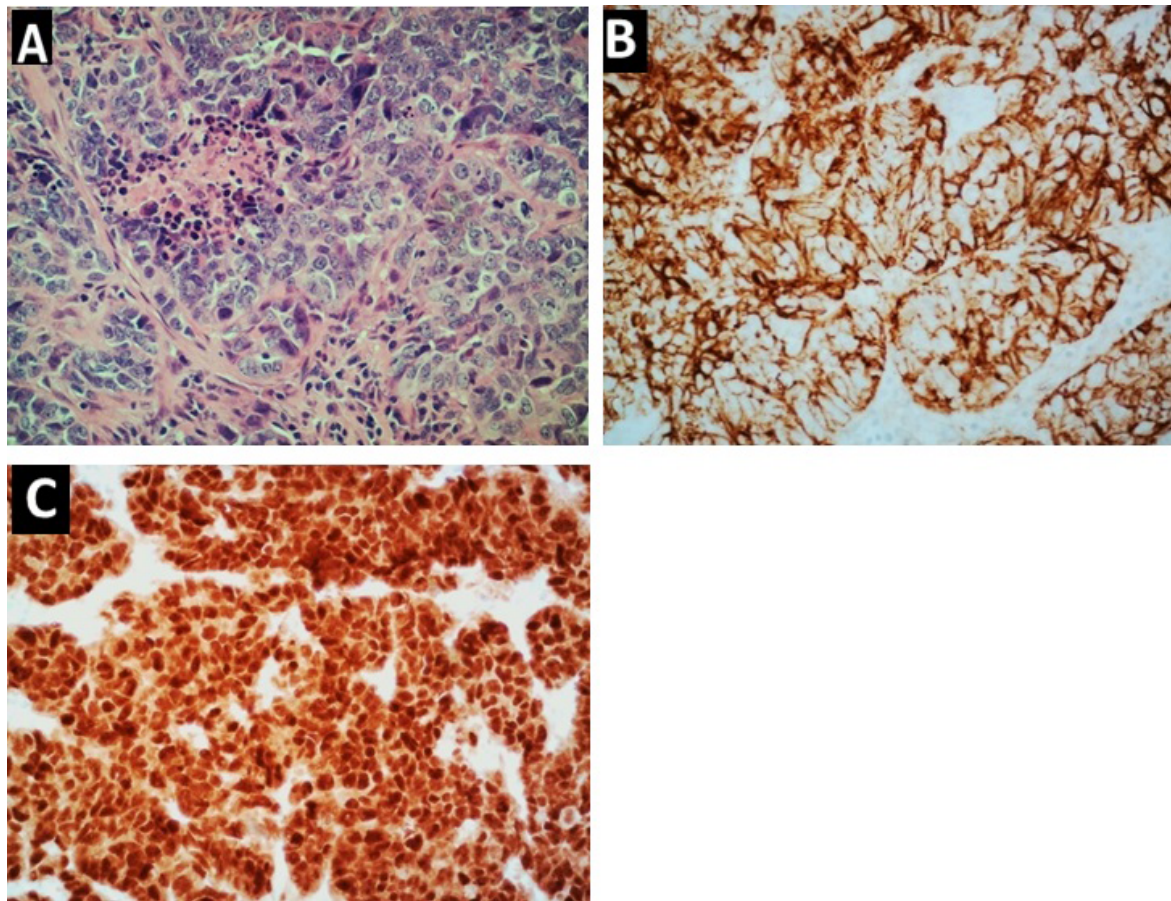


Figure 2. — Microscopic findings of the left supraclavicular LN mass. (A) Lymph node extensively replaced by poorly differentiated carcinoma with extensive necrosis (H&E Stain; $\times 200$) (B) Section stained with CA 125 ($\times 200$) (C) Section stained with PAX 8 ($\times 200$).

cases of PPC [7]. Satti *et al.* reported a case of fallopian tube cancer presenting as left supraclavicular lymphadenopathy [8]. The patient on staging showed left pelvic mass as well as para-aortic lymphadenopathy [8]. Yang *et al.* and Ang *et al.* reported cases of post-menopausal women presenting with isolated LN in the right groin [6, 9]. However, in both these cases, an ovarian primary tumour was found at exploratory laparotomy and the pathology confirmed papillary serous ovarian cancer [6, 9]. In neither of these cases was there extensive LN disease at surgery or on CT scan [6, 9]. There are also case reports of presentations with supradiaphragmatic LN involvement. Mason *et al.* report a case of ovarian cancer presenting with internal mammary metastases with peritoneal and hepatic metastases associated with an ovarian mass [5]. Nomoto *et al.* describe a case of PPC in a woman with a history of breast carcinoma presenting with metastases to left axillary lymph node who was also found to have peritoneal and liver metastases [10]. In all the cases cited above, and others reported in literature, the patients were either known to have ovarian cancer previously or found to have ovarian cancer on staging, including omental/peritoneal metastases.

Two cases of PPC reported by Kim *et al.* bear the closest resemblance to our case. They report two women presenting with palpable cervical lymphadenopathy in the neck with the biopsy showing metastatic serous adenocarcinomas [1]. In both cases, CT showed multiple areas of lymphadenopathy and a pararenal

mass [1]. The authors do not describe the extent and sites of LN involvement in these cases. Ours is the only case of PPC with a presentation radiologically mimicking lymphoma without the involvement of peritoneum or the ovaries.

This unusual pattern of presentation and spread poses many questions, clinical as well biological; (a) Does the predominantly nodal presentation have a different natural history and prognosis? (b) Does nodal spread indicate lymphatic spread of ovarian cancer is as important as transcoelomic spread? (c) Is this a form of skip metastasis? (d) Does the LN predominant PPC/ovarian cancer represent a distinct molecular subtype of serous ovarian/PPC?

PPC has long been thought to spread predominantly via transcoelomic route to peritoneum. However, this view has been challenged by experiments in animal models showing haematogenous spread as an important mode of spread of PPC through the ErbB3/NRG1 signalling pathway [11]. The most common sites of lymphatic involvement in ovarian carcinoma include the paraaortic and pelvic LNs [5]. As these nodes become involved, lymphatic channels running below the diaphragm will aid transfer across and above the diaphragm [6]. Biologically, the preferential involvement of LNs may be related to host-tumour factor or the microenvironment interaction driving survival and progression of cancer cells in LNs, rather than proceeding transcoelomically [12]. Our case, along with other reports cited above, of LN predominant distribution of disease suggest lymphatic

spread is as important as transcoelomic spread.

LN involvement appears to confer different prognosis in different settings. Legge *et al.* reported isolated LN relapse in ovarian cancers follow an indolent course, carrying better prognosis, as opposed to peritoneal/omental relapse [13]. In contrast, Bachmann *et al.* reported higher nodal involvement at cytoreductive surgery is associated with adverse prognosis [14]. The natural history of PPC/EOC presenting with LN predominant disease is unknown as such cases are uncommon. It is therefore unclear the prognostic significance of LN predominant PPC/EOC compared to the more common peritoneal dominant PPC/EOC.

Skip metastases have been well described in axillary nodal metastases from breast cancer with nodes involved distant from the sentinel node [10]. Is this a form of skip metastasis where the usual sites of spread such as peritoneum and omentum are bypassed or skipped for preferential seeding of LNs?

Tumour heterogeneity has been well recognised in several tumour types including breast and gastrointestinal cancer and has led to molecular sub-classification with distinct natural history and potential targets for treatment. Molecular sub-classification of EOC has been described with differing outcomes [15]. Our case might represent a molecular subtype of PPC/EOC with distinct biological and clinical features.

Conclusions

This case represents a unique presentation of PPC with an unusual mode of spread. It highlights important clinical and biological heterogeneous aspects of PPC and it is essential to bear in mind PPC in the differential diagnosis in women presenting with lymphadenopathy with pathology showing adenocarcinoma.

Authors' contributions

Rosie Clare: paper writing. David Agbamu: immunohistochemistry and pathological analysis and figure heading. Radhakrishnan Jayan: radiological analysis and figure heading. Eliyaz Ahmed: information gathering, clinical evaluation and paper writing.

Ethics approval and consent to participate

Written informed consent was obtained from the patient's next of kin (son) for this case report.

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Conflict of Interest

No authors have any conflict of interest to declare.

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