CASE REPORT

Locoregional recurrence of breast cancer presenting as upper limb venous thromboembolism

Anna Sayers,¹ Carla Hope,² Krishna M Lingam³

¹Surgical Specialties Division, Chesterfield Royal Hospital, Chesterfield, Derbyshire, UK
²King's Mill Hospital, Sutton-in-Ashfield, Nottinghamshire, UK
³Derby Hospitals NHS Trust, Derby, UK

Correspondence to
 Dr Anna Sayers,
 anna.sayers@nhs.net

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SUMMARY

Locoregional recurrence of breast cancer is a major concern for both patient and oncologist. Presentation as venous thromboembolism (VTE) carries risk of delayed diagnosis and has a poor prognosis. Here we describe, for the first time in the literature, a delayed diagnosis of local recurrence of infiltrative inflammatory breast cancer presenting as extensive deep venous thrombosis of the upper arm veins. This case demonstrates the need for a high level of vigilance for recurrence of malignancy in patients with no concurrent risk factors for VTE and atypical clinical progression in order to reach a timely diagnosis.

BACKGROUND

Inflammatory breast cancer (IBC) 5-year recurrence rates are estimated at 60% with survival rates at 40%.¹ The relationship between venous thromboembolism (VTE) and malignancy is well recognised, and a meta-analysis of 38 cohort studies estimated an incidence rate of 10 per 1000 person-years in active breast cancer. Chemotherapy and/or hormone therapy increase this risk further²; a large UK study reported the risk of VTE as 6% during chemotherapy and in the month after treatment.³ With respect to endocrine therapies, tamoxifen significantly increases the VTE risk, although aromatase inhibitors such as anastrozole do not. Presentation with VTE indicates poorer prognosis and a more advanced stage of disease.⁴ Upper extremity deep venous thrombosis (DVT) represents ~10% of total cases. It has a lower rate of recurrence and the risk factors differ compared with conventional VTE.⁵ The strongest independent predictor for an upper extremity DVT is an indwelling central venous catheter, and active or previous malignancy is also a significant factor.⁶

A 61-year-old woman presented with acute onset pain and new swelling in the right upper arm and shoulder. Ten years previously she was diagnosed with right-sided oestrogen receptor-positive breast inflammatory adenocarcinoma. This had been treated with wide local excision, axillary node sampling followed by chemotherapy (cyclophosphamide, methotrexate and 5-fluorouracil), radiotherapy and 5 years of anastrozole. Duplex sonography (US) revealed non-occluding thrombus in the mid-section and distal section of the subclavian vein and occluding thrombus in the axillary and brachial veins. CT showed extensive fat stranding and soft tissue swelling in the right shoulder and upper arm,

but no causative lesion was identified. The patient was initially diagnosed with idiopathic DVT and anticoagulated with enoxaparin. Symptomatic control was achieved with analgesia and she was discharged on rivaroxaban.

Three weeks later she re-presented to the emergency department with evolving pain and swelling extending to the upper neck. She was transferred to our tertiary centre for further management. On examination there was pitting oedema with limited range of movement and reduced fine motor dexterity. There was tenderness along the deep venous system in the upper arm and collateral superficial venous engorgement. Arterial pulses were palpable and breast examination found right-sided peau d'orange ([figure 1](#)).

INVESTIGATIONS

Repeat US confirmed the findings demonstrated on her first presentation. CT showed heterogeneous muscle oedema in the right upper arm and axilla that extended to the upper chest wall and lower neck ([figure 2](#)). Inflammatory markers, creatine kinase (CK), calcium and liver function tests were within laboratory reference ranges. Given her background, breast radiological and surgical reviews were sought. Based on the clinical findings, the specialist opinion was that there was no evidence of locoregional recurrence.

Her swelling continued to progress, resulting in paraesthesia, decreased sensation distally and significantly decreased fine motor skills. The unclear cause of her ongoing symptoms warranted further investigation. At the time the breast surgeons thought her unlikely to have recurrence of breast cancer. After multidisciplinary discussion with radiologists, MRI was performed to facilitate diagnosis. Appearances were non-specific, possibly representing myonecrosis, fasciitis or subcutaneous erythema. Subsequent core biopsy was taken under US guidance from a low echogenic area in the right tendon of biceps brachii comprising striated muscle, fibrous and adipose tissue. Histopathological examination confirmed poorly differentiated adenocarcinoma (cytokeratin-7 (CK7) and cytokeratin 5.2-positive, CK20 and estrogen receptor negative) ([figure 3A–C](#)), in keeping with local recurrence of infiltrative primary breast cancer and lymphoedema. Nuclear scintigraphy did not detect any suspicious bony lesion. However, the study was only partially tolerated due to positional pain.

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Figure 1 Right-sided arm and shoulder swelling, superficial venous engorgement and peau d'orange prior to radiotherapy.

DIFFERENTIAL DIAGNOSIS

DVT classically presents with acute pain and oedema, more commonly in a lower limb. The severity of her pain was disproportionate to a diagnosis of DVT, which initially prompted concerns of compartment syndrome. However, vascular examination was normal and the right arm remained well perfused. Normal inflammatory markers, CK levels and the duration of onset ruled out an autoimmune myositis.

Idiopathic VTE may be diagnosed in the absence of the following triggering circumstances:

- ▶ Major: plaster cast immobilisation and/or fracture of a lower limb or surgery under general anaesthesia lasting for more than 30 min or best rest for more than 3 days, occurring in three previous months or active cancer in the two preceding years
- ▶ Moderate or minor: pregnancy or postpartum, oestrogenic contraceptive or hormone replacement therapy in the year preceding the VTE, a journey lasting for more than 6 hours.⁷

No circumstances were evident; however, the history of ipsilateral IBC remained a concern, despite breast team opinion that there was no evidence for recurrence. The presence of peau d'orange characterised the swelling as lymphoedematous, although this was not recognised at initial presentation. This presented us with a dilemma, in so far as further investigation was namely to exclude locoregional recurrence of breast cancer. A second

radiological opinion resulted in a biopsy to ascertain the origin of the abnormal tissue seen on MRI. Consequently the patient's occult malignancy was identified, although a delayed diagnosis.

TREATMENT

Enoxaparin 1 mg/kg once daily for a minimum duration of 6 months was prescribed as initial management for DVT. For a brief period between breast team input and histological diagnosis, warfarin was started on haematological advice. Compression with tubular dressing, oral dexamethasone and radiotherapy with 20 grey in five fractions locally were started to treat the IBC and palliate her symptoms. In consideration of her previous tumour histological surface receptor profile, anastrozole was restarted.

OUTCOME AND FOLLOW-UP

Her symptoms improved and she was discharged home with a plan to begin six cycles of chemotherapy FEC75 (5-fluorouracil, epirubicin, cyclophosphamide) as an outpatient. She was readmitted to hospital acutely hypoxic after her second cycle of chemotherapy. Pulmonary embolism was ruled out by CT pulmonary angiogram and she received treatment for *Pneumocystis jiroveci* pneumonia.

DISCUSSION

To the best of our knowledge there have been no previous reports of breast cancer recurrence presenting as DVT in the upper limbs. There was no evidence on initial examination or investigation for recurrence; however, the progressive oedematous swelling raised clinical suspicion and led to further investigation with MRI and tissue biopsy. Biopsy samples were taken from the biceps brachii due to notable heterogeneity demonstrated at the time by US. The high recurrence rate of IBC was enough to provoke a high index of suspicion in this case. Recurrent IBC can be difficult to detect radiologically, and diagnosis is largely based on clinical findings. Mammography and ultrasound findings are varied and include skin thickening, increased tissue density and mass.⁸ However, these radiological findings are non-specific. Some studies report high detection rates of primary IBC with MRI and can be useful to identify a site for punch biopsy.⁹

The incidence of idiopathic first VTE varies from ~25% to 50% between studies.¹⁰ The risk of cancer within the first 2 years in patients presenting with first apparent idiopathic VTE, however, is significant. A Swedish population-based study of almost 62 000 showed a standardised incidence ratio of 4.4.¹¹ A meta-analysis reported a threefold increase in the presence of occult cancer following a diagnosis of VTE.¹² In a patient diagnosed with an unprovoked VTE, the National Institute for Health and Care Excellence (NICE) guidelines recommend a guided physical examination, a chest X-ray, blood tests (full blood count, liver function tests and serum calcium) and urinalysis. This combination has been shown to detect half of all cancer. In all patients aged over 40 years, an abdominopelvic CT scan and a mammogram in women should be considered if there are no signs of cancer on initial investigation.¹³ Undoubtedly her diagnosis would have been further postponed had we not investigated further in spite of discordant expert opinions.

Only three cases of DVT as first presentation of primary breast cancer were identified in the literature.^{14–16} Hypercoagulability in malignancy is well recognised, although the mechanisms are not comprehensively understood. Virchow's triad describes the pathophysiology of thromboembolic disease. Malignant cells promote a hypercoagulable state by secreting proinflammatory

Figure 2 CT demonstrating heterogeneous oedema in the muscle and subcutaneous tissues of the arm and chest wall.

and procoagulant factors, and upregulating coagulation-dependent receptors. In this particular case, malignant infiltration surrounding, and into, the vasculature and lymphatic system likely contributed to haemostasis. Third, endothelial cell function is compromised by the loss of antithrombotic mechanisms, downregulated in response to inflammation.^{17 18} The current NICE guidance for the treatment of VTE in patients with cancer is low molecular weight heparin for 6 months, after which time the need for continued anticoagulation should be re-evaluated. At present, there is insufficient evidence to evaluate the use of new oral anticoagulants for the treatment of cancer-associated VTE.¹⁹

IBC has a high 10-year recurrence rate and soft tissue metastases are not unknown. Local and distant soft tissue 10-year recurrence rates have been estimated at 15.6% and 10.6%, respectively.¹ In this patient who was not clinically responding to treatment, it was important to revisit the differential diagnosis and her significant medical history. In any patient with a background of IBC presenting with atypical symptoms, recurrence should be suspected until excluded. Furthermore, if the peau d'orange found on examination had been considered in full, the

Figure 3 Right tendon of biceps brachii tissue biopsy showing (A) poorly differentiated adenocarcinoma cells, (B) strong cytokeratin 5.2 staining in the majority of tumour cells and (C) a subset of cells positive for cytokeratin-7.

diagnostic strategy that followed would have been circumvented and a diagnostic punch biopsy of the skin performed earlier. Tissue sampling is the only definitive way to exclude or prove recurrence, and any suspicious clinical or radiological findings should be considered for biopsy.

Anastrozole was restarted despite the tumour tissue biopsy testing ER-negative. We are unaware of any evidence to support its use in true ER-negative tumours; however, immunohistochemical analysis is subject to a high false-negative rate at least 20%.²⁰ Given the primary tumour was ER-positive, the oncologists felt repeat biopsies would be unnecessary. The patient had tolerated anastrozole well previously, and it could potentially benefit her if ER were indeed present.

Learning points

- ▶ Venous thromboembolism (VTE) can be the first presentation of cancer or recurrence of cancer.
- ▶ Atypical DVT should carry a higher level of clinical suspicion for underlying malignancy.
- ▶ Inflammatory breast cancer carries a high recurrence rate, and in patients with inexplicable symptoms recurrence should be excluded.
- ▶ Punch biopsy of the lymphoedematous breast skin examining for inflammatory breast cancer would have been an appropriate after finding peau d'orange.

Contributors AS, First and corresponding author. CH, Second author. KML, Consultant responsible.

Competing interests None declared.

Patient's perspective

"I think my lymphoedema and stiffness should have been noted at first presentation. I went from Rivaroxaban to Enoxaparin to Warfarin [without improvement]... Doctors were 'not willing to change their thought pattern.'"

Patient consent Obtained.

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