Ovarian malignancy revealed by anticoagulation

Introduction

The awareness of venous thromboembolism has increased in recent years with many cases being recognized early and appropriately managed. However, the precipitating features for these 'unprovoked' thromboses are often not identified. Malignancies are one of the strong thrombotic risk factors which precipitate the development of venous clots. However, not uncommonly, the malignant condition may present at a later date than the thrombotic complication it triggered.

Discussion

This case is relevant from three important clinical points. First, malignancy is a very strong risk factor for thrombosis. Second, an episode of thrombosis can predate the diagnosis of cancer, and last, haemorrhagic episodes are uncommon in patients on anticoagulation unless bleeding has started for a different reason.

Malignancies including gynaecological cancers are strong risk factors for thrombosis. The pathophysiology underlying this increased risk is thought to be tissue factor production by the tumour, which facilitates invasion and metastasis, but also activates the coagulation cascade. Gynaecological cancers are thought to be exceptionally high risk in developing venous thromboembolism. In particular, the highest incidence of venous thromboembolism is with ovarian cancer where an incidence of 120/10 000 has been reported from the United States (Levitan et al, 1999). These patients are also at particular risk for postoperative pulmonary emboli, on average 14 times more likely than in those undergoing surgery for benign disease. Again, the highest incidence was in those with ovarian cancer, where 6.8% of patients experienced a pulmonary embolism in the first fifty postoperative days compared to 0.3% with benign disease (Martino et al, 2006).

Interestingly, it has also been postulated that the characteristics of pulmonary emboli in patients with malignancy are different to those of patients who do not have a malignancy. A small retrospective study showed that the incidence of central pulmonary emboli is higher in cancer-related pulmonary emboli, with a modestly increased odds ratio (2.08, 95% confidence interval 1.06–4.10) (Hasenberg et al, 2009).

In a large population study, approximately 11% of patients with unprovoked venous thromboembolisms were eventually diagnosed with cancer after a delay of 1–2 years (Baron et al, 1998). During admission or in the first year, the standardized incidence ratio for cancer was 3.2 (95% confidence interval 3.1–3.4) and the risk remained high until 10 years after the unprovoked venous thromboembolism. The risk was more pronounced in patients under 65 years of age (Baron et al, 1998). As a result, National Institute for Health and Care Excellence (2012) guidance recommends a number of investigations for cancer in individuals with unprovoked pulmonary embolism. All patients with an unprovoked pulmonary embolism should have baseline investigations (physical examination, full history, urinalysis, chest X-ray, full blood count, serum calcium and liver function tests). Additionally, for patients over the age of 40 years, regardless of the baseline investigations, an abdomino-pelvic computed tomography scan and mammogram for women should be considered (National Institute for Health and Care Excellence, 2012).

While malignancies cause increased risk of venous thromboembolism, they also often confer a bleeding risk as a result of local invasion of adjacent vessels and neovascularization (Pereira and Phan, 2004). Anticoagulation in this case unmasked a

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Case Report

A 51-year-old Caucasian woman presented to accident and emergency with pleuritic chest pain and shortness of breath, prompting a diagnosis of bilateral pulmonary emboli on computed tomography pulmonary angiogram. There were no clearly identifiable risk factors for thrombosis. She was treated with warfarin for an episode of unprovoked venous thromboembolism. The patient was readmitted a month later with abdominal pain localizing to the left flank. Despite the absence of any overt bleeding, her haemoglobin level was 51 g/litre for which she received 4 units of blood. Computed tomography scan (*Figures 1a* and *1c*) revealed a peritoneal haematoma (16 cm in diameter). In light of the haematoma in a person with recent thrombosis, anticoagulation was changed to dalteparin for its more predictable pharmacokinetics. Transvaginal ultrasound showed the haematoma to be in the region of the left ovary, in addition to two fibroids. Hysteroscopy revealed no abnormalities apart from a small polyp on the anterior endometrium. Excision of the polyp or biopsy was not attempted at the time as she was being anticoagulated.

However, a magnetic resonance imaging scan of the pelvis (*Figures 1b* and *1d*) a month later showed a mass on the ovary, which was initially suspected to represent the remnant haematoma. Six months after the initial presentation, performing a total abdominal hysterectomy and bilateral salpingo-oophorectomy was discussed. Postoperative histology revealed a clear cell carcinoma of the ovary with confirmation from pelvic fluid cytology (stage 2C). Adjuvant chemotherapy in the form of paclitaxel and carboplatin was given. There was no evidence of disease on the end of treatment scan. As the ovarian malignancy was thought to be the precipitating factor for the embolism, anticoagulation was discontinued and she remained thrombosis-free at 6 months review. The patient had no significant past medical history, was a non-smoker and occasionally drank alcohol. Thrombophilia screening was negative. There was no family history of thrombosis, but the patient's first cousin had ovarian cancer.

symptomatic haematoma, which may otherwise have been a slow, low-volume local bleed, prompting further investigation. It is important to note that anticoagulation normally does not cause a spontaneous bleed, but merely increases the blood volume in the event of a pre-existing haemorrhage. A similar principle applies to menstrual blood loss, where oral anticoagulants may increase the blood volume lost but are not closely associated with the development of menorrhagia (van Eijkeren et al, 1990). Therefore, changes in menstrual patterns should not necessarily be attributed to the initiation of oral anticoagulants, and should instigate further investigation. BJHM

Baron JA, Gridley G, Weiderpass E, Nyren O, Linet M (1998) Venous thromboembolism and cancer. *Lancet* **351**: 1077–80

Hasenberg U, Paul T, Feuersenger A, Goyen M, Kröger K (2009) Cancer patients and characteristics of pulmonary embolism. *Eur J Radiol* **69**: 478–82 (doi:10.1016/j.ejrad.2007.11.022)

Levitan N, Dowlati A, Remick SC et al (1999) Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy: risk analysis using Medicare claims data. *Medicine* **78**: 285–91

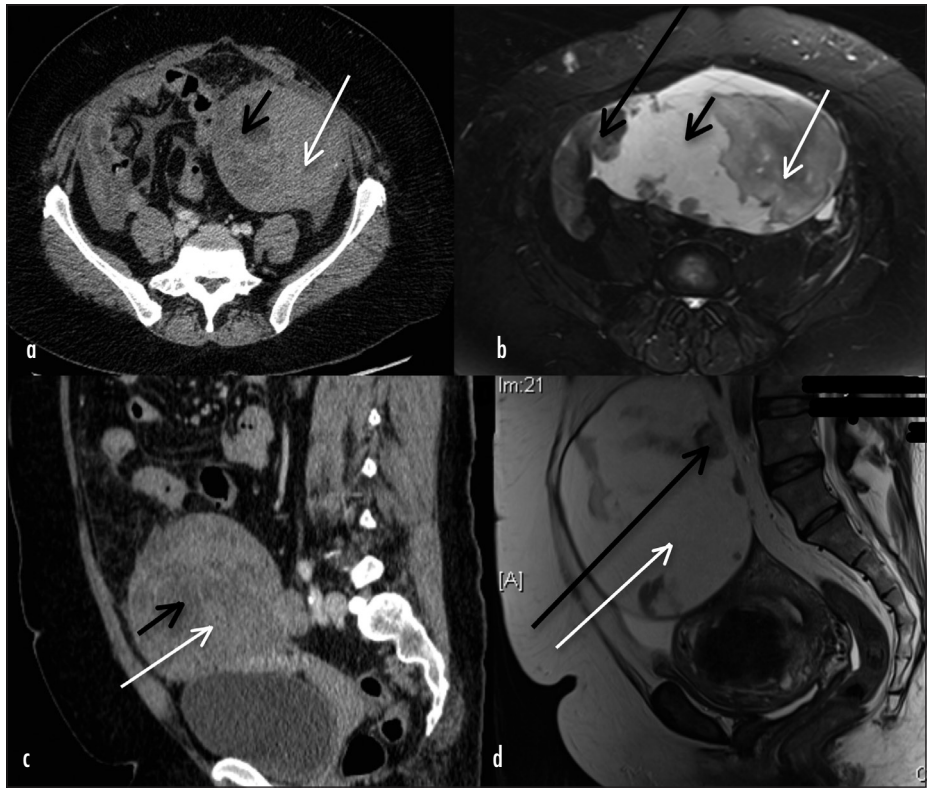
Martino MA, Borges E, Williamson E et al (2006) Pulmonary embolism after major abdominal surgery in gynecologic oncology. *Obstet Gynecol* **107**: 666–71

National Institute for Health and Care Excellence (2012) Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. www.nice.org.uk/guidance/cg144 (accessed 25 July 2014)

Pereira J, Phan T (2004) Management of bleeding in patients with advanced cancer. *The Oncologist* **9**: 561–70 (doi: 10.1634/theoncologist.9-5-561)

van Eijkeren MA, Christiaens GC, Haspels AA, Sixma JJ (1990) Measured menstrual blood loss in women with a bleeding disorder or using oral anticoagulant therapy. *Am J Obstet Gynecol* **162**: 1261–3 (doi: 10.1016/0002-9378(90)90031-2)

Figure 1. Imaging showing haematoma originating from left ovary. a. Axial computed tomography. b. Axial T2 weighted magnetic resonance imaging. c. Sagittal computed tomography. d. Sagittal T1 weighted magnetic resonance imaging. Black long arrow: solid tumour. Black short arrow: cystic component. White arrow: haemorrhagic component with solid tumour.



LEARNING POINTS

- The incidence of unprovoked venous thromboembolism in gynaecological malignancy, in particular ovarian cancer, is high.
- Gynaecological symptoms in conjunction with an unprovoked venous thromboembolism should heighten suspicion of gynaecological malignancy and prompt more urgent investigation.
- Unprovoked bleeding with warfarin and other anticoagulants is rare. Anticoagulation may promote more substantial blood loss in the event of a haemorrhage, but not act as a spontaneous cause.