Myeloid sarcoma of uterine cervix: A case report with review of the literature

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ARTICLE INFO

Keywords:
Myeloid sarcoma
Uterine cervix
Acute myeloid leukaemia

ABSTRACT

Myeloid sarcoma is a rare clinical entity, characterised by the extramedullary presence of myeloblasts. It can occur de novo or signify disease recurrence. Involvement of the female reproductive tract is uncommon, with most cases described in the literature occurring in the uterus or ovary. We present an unusual case of myeloid sarcoma of the uterine cervix diagnosed incidentally in a patient with cervical-intraepithelial neoplasia grade 2 (CIN2), followed by a literature review.

1. Introduction

Myeloid sarcoma is a rare malignancy, characterised by the extramedullary presence of myeloblasts. It can affect various anatomical sites. It may occur de novo, with concurrent acute myeloid leukaemia (AML) or herald disease relapse. Involvement of the female reproductive tract is uncommon with most cases described in the literature occurring in the uterus or ovary. We present an unusual case of myeloid sarcoma of the uterine cervix that was diagnosed as an incidental finding in a patient with CIN2, followed by a literature review.

2. Case presentation

A 26 year old para 1 + 0 was referred with severe dyskaryosis. A loop excision of transformation zone showed koilocytosis and grade 2 cervical intra-epithelial neoplasia (CIN2). An unexpected incidental finding was a space-occupying lesion in the subepithelial tissue (Fig. 1A). The lesion consisted of sheets of medium sized blast-like cells with hyperchromatic nuclei, a rather fine chromatin and high nuclear to cytoplasmic ratio (Fig. 1B). Immunohistochemistry showed the cells were strongly positive for MPO, CD33, CD117 and BCL-2 (Fig. 2A, 2B, 2C). There was variable expression of CD45, CD15 and CD30 (Fig 2D). The cells were negative for CD34, pancytokeratins, B and T cell lymphoid markers. P16 overexpression was seen within CIN2 with some patchy non-specific staining within subepithelial lesional tissue. The features were consistent with a myeloid sarcoma involving the uterine cervix.

Further investigation showed her blood count was unremarkable aside from mild eosinophilia (white cell count (WCC) 9.0 × 10⁹/L, neutrophils 5.12 × 10⁹/L, eosinophils 0.47 × 10⁹/L, monocytes 0.63 × 10⁹/L). A bone marrow aspirate was a dry tap, precluding additional investigations, trephine did not show an excess of blasts. She was treated with two cycles of DA (daunorubicin/cytarabine) and two cycles of high dose cytarabine as part of the AML19 trial, concluding in May 2017. Bone marrow aspirates following cycle 1 and end of treatment were consistent with complete remission (CR), with some mild dyserythropoietic changes in keeping with bone marrow regeneration following chemotherapy. At the conclusion of intensive chemotherapy, the patient underwent colposcopy which showed no evidence of malignancy and an ultrasound scan 12 months post treatment showed no pathology.

She remained in clinical remission for 30 months when she presented with a history of pharyngitis, fever and malaise. Initial investigations demonstrated anew pancytopenia (Hb 107 g/L, platelets 52 × 10⁹/L, WCC 14.5 × 10⁹/L, eosinophils 0.02 × 10⁹/L and neutrophils 0.15 × 10⁹/L) with circulating myeloblasts noted on blood film examination. Repeat aspirate was aparticulate. Immunophenotyping showed the peripheral blood blasts were positive for HLADR, CD117, CD33 and intracellular MPO. Bone marrow trephine revealed heavy infiltration by...
acute leukaemia with sheets of medium sized blasts (Fig. 3). The blasts were positive for MPO and CD117 with a subset expressing TdT, similar to the blasts noted on her original myeloid sarcoma biopsy. Cytogenetic analysis revealed a normal karyotype. Molecular analysis showed the presence of nucleophosmin 1 (NPM1) positive (type A mutation) and FLT3-ITD negative.

She was subsequently treated as per the high risk arm of AML19, a trial aimed at younger individuals with acute myeloid leukaemia. She received a cycle each of FLAG-Ida (fludarabine, cytarabine, lenograstim, idarubicin) and MACE (amsacrine, cytarabine, etoposide) before undergoing a matched sibling donor peripheral blood stem cell allogeneic transplant with cytarabine and total body irradiation conditioning. She was transplanted in molecular remission. At the time of writing of this report, >18 months post transplant, she remains in clinical, morphological and molecular remission.

Fig. 1. (A) Microscopic examination of the LLETZ specimen showed CIN2 with an underlying space occupying lesion. (B) Higher magnification showing infiltration of the subepithelial tissue by sheets of medium-sized blasts with readily identified mitotic figures (H&E, X 20).

Fig. 2. Tumour cells were strongly positive for MPO (A), CD33 (B) and CD117 (C) with variable expression of CD45 (D) (X 20).

Fig. 3. Bone marrow trephine showing heavy infiltration by sheets of blasts, consistent with AML relapse. (H&E, X 20).
3. Discussion

Myeloid sarcoma (MS) describes a tumour mass consisting of myeloid blasts occurring at an anatomical site out with the bone marrow (BM). It can occur in isolation or precede the onset of leukaemia and is described as non-leukaemic MS in such cases (Kahn et al., 2019). It is important to note that almost half of all patients with non-leukaemic MS will develop acute leukaemia with reported intervals of 5–11 months (Yamauchi and Yasuda, 2002). The tumour classically displays high levels of myeloperoxidase expression, lending its greenish colour, hence its historical name of chloroma (Magdy et al., 2019). Diagnosis can be challenging if presenting at an unusual site. Historically patients were misdiagnosed with other malignancies including lymphoma or non-haematopoietic neoplasms. Wide use of immunohistochemistry has resulted in less misdiagnoses and allowed early diagnosis and management (Almond et al., 2017).

Recognised anatomical sites include skin, bone, gastrointestinal tract and lymph nodes with differing anatomical sites associated with differing prognoses (Goyal et al., 2017). Involvement of the gynaecological tract is uncommon with less than 100 cases reported in the literature (Garcia et al., 2006). In a case series of 11 patients, Garcia and colleagues note that the uterus was the most frequently involved gynaecological anatomical site (8 patients): of whom three had cervical myeloid sarcoma (Garcia et al., 2006). Conversely, a small number of cases of MS of the uterine cervix have been reported previously—these typically serve as sanctuaries for leukaemic cells and allow them to evade systemic therapy (Bakst et al., 2011). The mechanism by which myeloblasts can involve the reproductive tract is not well elucidated, and may reflect adhesion receptors such as CD56, or due to these sites serving as sanctuaries for leukaemic cells and allow them to evade systemic therapy (Bakst et al., 2011). A small number of cases of MS of the uterine cervix have been reported previously—and usually present with vaginal or postcoital bleeding, reflecting tissue infiltration. Systemic manifestations including fever, night sweats and weight loss are also recognised (Garcia et al., 2006).

Prognosis is generally poor, with 2 year survival rates of 6% reported (Pathak et al., 2005). The use of systemic therapy with agents used for treating AML is widely accepted. The optimal therapy for non-leukaemic MS is still unclear, although previous analysis shows that the development of leukaemia can be delayed in those who receive systemic chemotherapy when compared to resection or local radiotherapy (Tsimberidou et al., 2008). In addition, in patients treated with chemotherapy including cytarabine and an anthracycline (as in our case), the period of progression to acute leukaemia was longer than those treated with lymphoma regimens.

Haematopoietic stem cell transplant (HSCT) is associated with an improved outcome. In a case series by Pileri et al., MS patients treated with autologous or allogeneic HSCT corresponded with long term survivors compared with those treated with conventional chemotherapy (overall survival at 2 years 76% vs 9%) (Pileri et al., 2007).

Interestingly in our case, the co-presence of HPV infection and CIN2 with myeloid sarcoma is noted. There is no known association between HPV infection and myeloid sarcoma of the uterine cervix documented in the literature. Missaoui et al. conducted a retrospective review of rare cancers of the uterine cervix and their link with HPV infection using in situ hybridization and immunohistochemistry for p16INK4a. There was no evidence of overexpression of p16INK4a in their myeloid sarcoma case (Missaoui et al., 2018).

Our patient was NPM1 positive in the absence of FLT3-ITD. In a case study of 181 MS patients by Falini et al, NPM1 was the most frequent molecular abnormality detected, seen in 15% patients by immunohistochemistry. It usually corresponded with a lack of CD34 expression and normal karyotype as in this case (Falini et al., 2007). Whilst in AML the presence of NPM1 mutation in the absence of FLT3-ITD confers a favourable prognosis, it appeared to be a negative prognostic indicator in MS with only 3 of 26 patients with NPM1 mutation being alive at time of follow up with a median follow up of 15 months (Falini et al., 2007). In 5 of 14 patients with de novo MS, bone marrow involvement was documented within 6 months of the diagnosis of MS. In 6 of 26 patients diagnosis of MS and AML was concurrent and in 5 of 26 patients MS was subsequent to diagnosis of AML.

In conclusion, we present a case of myeloid sarcoma of the uterine cervix, presenting unexpectedly in a patient with CIN2. Our case highlights the importance of considering myeloid sarcoma in the differential diagnosis of undifferentiated malignant tumours of the cervix to allow early diagnosis and management. Our patient had no evidence of systemic disease at presentation but relapsed with NPM1 positive AML two years following intensive AML therapy.

4. Consent

An informed written consent was obtained from the patient for publication of this report and accompanying images.

CRediT authorship contribution statement

C. Mullen: Data curation, Writing – original draft. S. Beverstock: Writing – review & editing. H. Roddie: Writing – review & editing. V. L. Campbell: Writing – review & editing. W. Al-Osous: Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This paper did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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