

Paraneoplastic leukemoid reaction in advanced cervical cancer- an uncommon diagnosis.

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INTRODUCTION

A paraneoplastic leukemoid reaction is a reactive haematological disorder characterized by leukocytosis greater than $50 \times 10^9/L$ associated with non-haematological malignancy [1,2]. There is a marked increase in neutrophils within the peripheral blood with left shift of the myeloid lineage. It is relatively common in solid tumors, but very rare in gynecologic malignancies. There have not been many published cases of patients with cervical cancer presenting with this abnormality, therefore the clinical and prognostic significance of leukocytosis in this tumor type is relatively unknown. Here, we present a case of paraneoplastic leukemoid reaction occurring in a young woman with an advanced stage squamous cell cervical cancer.

CASE REPORT

A 35-year-old female was referred to the colposcopy unit with a history of post-coital bleeding. A cervical pap smear showed high grade dyskaryosis. She had a previous subtotal hysterectomy for uncontrolled haemorrhage following a medical termination of pregnancy. Unfortunately, she defaulted from all cervical screening thereafter. There were no other significant medical co-morbidities. On vaginal examination, she was found to have a bulky cervix with a polypoidal, friable, 6cm cervical mass with upper vaginal involvement. A cervical biopsy showed an invasive, moderately differentiated (grade 2) squamous cell carcinoma. On radiological imaging, the tumour extended to the left parametrium as well as the upper vagina but no distant metastases were identified. Following a multidisciplinary team discussion, the patient was referred for chemoradiation. Prior to starting the treatment, she developed severe lower back pain refractory to analgesia. Blood investigations revealed severe leukocytosis with a white blood cell count (WBC) of $67.1 \times 10^9/L$, (neutrophils:88.7%, lymphocytes:3.7%), haemoglobin 86g/L, platelets $591 \times 10^9/L$, and normal clotting function. Renal and liver function tests were within normal limits. She was also persistently tachycardic and pyrexia with a temperature of 38.90C. She was suspected of having a pyelonephritis and was started on broad spectrum antibiotics after a septic screen was performed. After 48hrs of antibiotic therapy, she was afebrile and the septic screen was negative. However, her WBC continued to increase, rising to $91 \times 10^9/L$. Another septic screen together with a blood film was performed along with microbiology and haematology consultations. The peripheral blood film revealed anisocytosis, hypochromia, rouleaux formation, polychromasia with platelet clumps, left shift in neutrophils with toxic granulation, vacuolation and marked leukocytosis (90% neutrophils) (Figure 1a). Following this, a bone marrow biopsy was performed and this showed increased myelopoiesis and megakaryopoiesis with marked left shift in these lineages. Although there were numerous immature cells present, there was also evidence of cellular maturation in keeping with a reactive process (Figure 1b). These overall features were suggestive of a leukemoid reaction. The repeat septic screen was again negative.

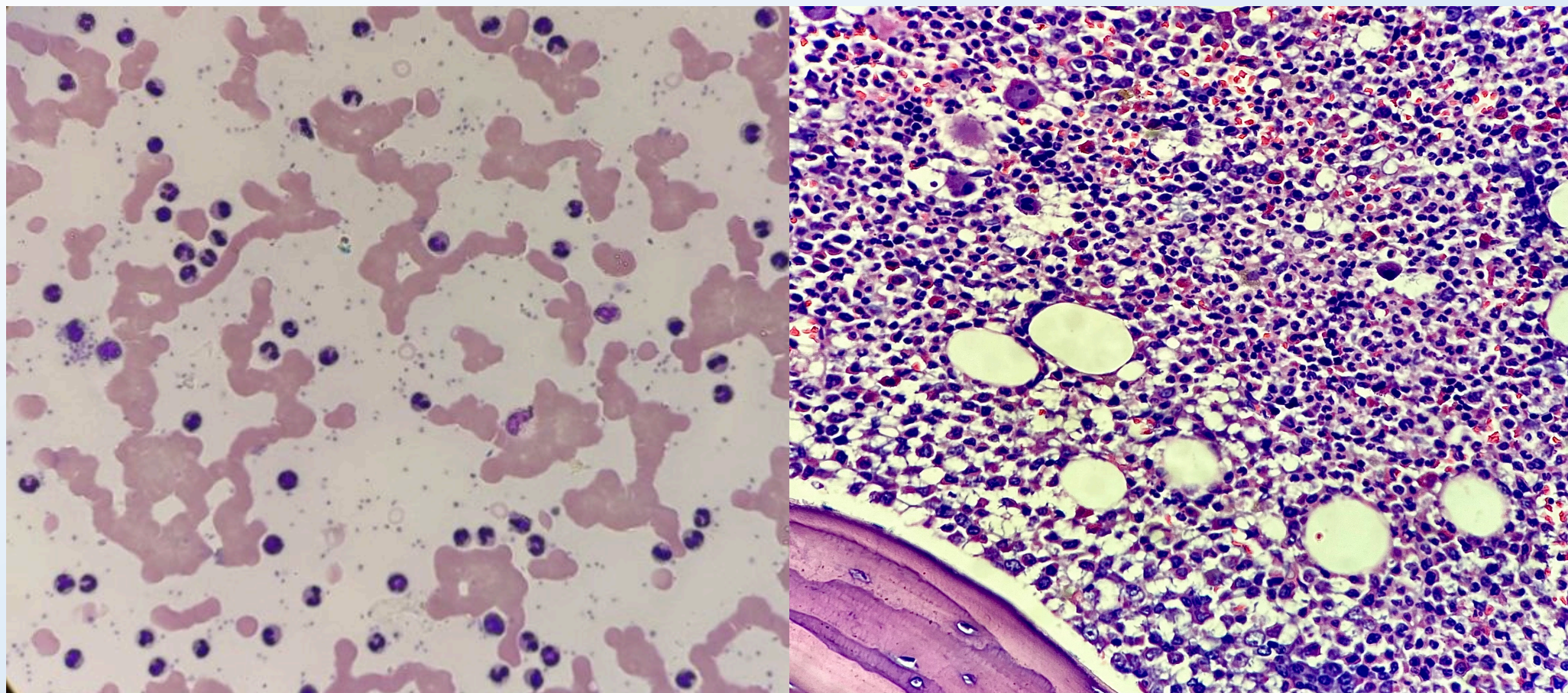


Figure 1
1a: Peripheral blood film showing numerous band form neutrophils and neutrophilic metamyelocytes. Toxic granulation and vacuolisation is noted within the neutrophils. x500
1b: Trephine bone marrow biopsy showing increased myeloid cells. There is evidence of lineage maturation with mature forms present. x400

Following another multidisciplinary meeting, it was decided to proceed with the first cycle of chemotherapy despite the high white cell count as there was no evidence of active infection. She continued to deteriorate despite treatment. Her WBC count rose to $192 \times 10^9/L$ and her haemoglobin fell to 48g/L. Repeat imaging showed marked disease progression with widespread metastases and extensive lymphadenopathy. She received multiple careful blood transfusions and was treated for hyperuricaemia and renal impairment. Palliative care was initiated when there was progressive deterioration of her clinical state. Unfortunately, the patient succumbed to her disease.

DISCUSSION

A paraneoplastic syndrome refers to a group of symptoms that occurs in patients with malignancy which cannot be explained by local invasion, distant metastasis, or the elaboration of hormones indigenous to the tissue of origin of the tumour [1]. It most commonly occurs in patients with lung cancer. According to Sakka et al 2006, a leukemoid reaction can be defined as a persistent leukocytosis in the absence of a hematologic malignancy [2]. When this leukemoid reaction occurs due to the presence of a non-haematolymphoid cytokine-secreting tumour in the absence of bone marrow infiltration by that solid tumour, it is known as a paraneoplastic leukemoid reaction [3]. Paraneoplastic leukemoid reactions (PLR) are caused by an alteration in the immune response to a neoplasm and are rarely seen in gynecologic malignancies. The most commonly secreted cytokine in PLR is the granulocyte colony-stimulating factor (G-CSF). However, there are other associated cytokines, some of which promote tumour growth and metastasis [4]. PLR can occur in conjunction with other paraneoplastic syndromes, such as the production of parathyroid hormone-related protein, leading to combined hypercalcaemia and leucocytosis which could further worsen prognosis [5].

Paraneoplastic leukemoid reaction most commonly presents with fever and symptoms of the underlying malignancy [6]. This presentation often leads to a diagnostic dilemma, as the elevated white blood cell count is thought to be due to an underlying infection or possibly a myeloproliferative disorder. While this can delay the appropriate treatment, a diagnosis of PLR can only be made after other causes of leucocytosis have been excluded. Our patient was initially suspected of having pyelonephritis and was treated with broad spectrum antibiotics which improved her pyrexia, but had no effect on her WBC, which actually worsened. The worsening of her leucocytosis, with a WBC $> 100 \times 10^9/L$, is referred to as hyperleukocytosis and is considered to be a medical emergency [7,8]. The standard care for this condition includes cytoreduction, proper supportive care, and treatment of tumour lysis. Packed red blood cells must be given with caution as they can significantly increase blood viscosity. Haemodynamically stable patients should have careful packed red transfusions when the haemoglobin level is less than 7-8 g/dl, avoiding post-transfusional levels above 10 g/dl. With haematologic consultation, this was taken into consideration when our patient was transfused as her haemoglobin level was very low. Also, she required treatment for her tumour lysis which resulted in hyperuricaemia.

Distinguishing leukemoid reaction from other diagnoses such as chronic myeloid leukaemia (CML) can be difficult. The absence of earlier granulocytic precursors (blasts and promyelocytes) can also aid in leaning toward a diagnosis of leukemoid reaction over CML [9]. Reactive granulocytes are also more frequently seen in leukemoid reactions. There are also additional investigations such as cytokine plasma levels which are not readily available at most institutions. The blood film for our patient did not contain granulocytic precursors, and had toxic granulation and vacuolation which is typically seen in leukemoid reaction.

Cervical cancer patients with leucocytosis tend to be younger as was seen in our patient who was aged 35years. It also occurs with large and more advanced stage cancers, and is also associated with poorer response rates to radiation [10]. This was also seen in our case as our patient had a large 6cm tumour. There is an associated increased case-fatality rate up to 76% within 12 weeks, 89% within 1 year, the remaining 10% of the patients who survived more than 1 year had received aggressive chemotherapy or surgery for the tumour [11]. This poor prognosis is due to the high levels of several inflammatory cytokines, especially G-CSF, which create a microenvironment that promotes carcinogenesis and tumour progression [10]. Therefore, the higher the leukocytosis suggests higher circulating G-CSF levels, the more likely the tumour will progress and therefore the worse the prognosis.

CONCLUSION

Paraneoplastic leukemoid reaction is rare in gynaecological malignancies, but is associated with a poor prognosis and decreased survival rates. There should therefore be a high level of clinical suspicion in cancer patients presenting with severe leucocytosis in the absence of infection.

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