CASE REPORT

Persistent sacral chloroma in refractory acute myelogenous leukaemia

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SUMMARY

Acute myelogenous leukaemia (AML) is a clonal process involving the myeloid subgroup of white blood cells. Chloromas, or myeloid sarcomas, are masses of myeloid leukaemic cells and are a unique aspect of AML. This case involves a 14-year-old boy with AML who presented with multiple chloromas at diagnosis. The patient's extra-calvarial masses and bone marrow involvement responded to chemotherapy; however, his sacral epidural chloromas persisted despite four courses of chemotherapy. The central nervous system, bone marrow and testes have been known to be sanctuary sites for AML. This case illustrates that the sacral spinal canal may potentially be a sanctuary site for the disease process also.

BACKGROUND

Acute myelogenous leukaemia (AML) is a clonal process that involves the myeloid, monocytic, erythroid and megakaryocytic subgroups of white blood cells (WBCs). AML accounts for approximately 10%–15% of childhood leukaemias and is traditionally diagnosed when myeloblasts account for greater than 20% of the bone marrow nucleated cells. The current WHO classification subdivides AML according to if the AML is due to prior radiation therapy or chemotherapy (t-AML), if the child has Down syndrome (DS-related AML), if there are any genetic abnormalities (eg, AML with t(8;21); inv(16); t(15,17); MLL rearrangements or prior myelodysplastic syndrome (MDS) or MDS-related mutations such as del(5q) or monosomy 7. If none of these criteria are met, AML is then diagnosed as not otherwise specified and subclassification reverts back to the morphological categories of the French-American-British (FAB) system.¹

Certain conditions predispose patients to acquiring AML.² Down syndrome patients have an increased risk of acute megakaryocytic leukaemia as well as acute lymphoblastic leukaemia.² Other inherited conditions like Noonan syndrome and neurofibromatosis type 1 also increase the risk of developing AML.² Bone marrow failure syndromes such as Kostmann syndrome, Diamond Blackfan anaemia, Fanconi's anaemia or dyskeratosis congenita have been shown to progress to MDS and/or AML.² Almost all abnormal DNA-repair syndromes, including ataxia-telangiectasia, Bloom syndrome and Li-Fraumeni syndrome have been shown to increase the risk of developing AML.²

A unique process of myeloid leukaemias includes the potential of developing discrete masses known as chloromas or myeloid sarcomas. Chloromas are more commonly diagnosed in patients younger than 10 years of age or between 20 and 44 years of age.³ They may be present at diagnosis or appear during relapse.⁴

Intensive, systemic chemotherapy administration for chloromatous disease has been shown to be the most effective treatment strategy.^{5–7} However, it is well known that the central nervous system (CNS) and testes are sanctuary sites for AML. In this case, epidural sacral chloromatous involvement in the spinal canal may have proven to be a sanctuary site for the disease as there were incongruent responses to therapy for this site compared with the other sites of disease.

CASE PRESENTATION

A 14-year-old boy presented to our emergency department for headaches and urinary incontinence. He had flu-like symptoms (nasal congestion, cough, rhinorrhoea and fever) for 4–5 days several weeks prior to presentation. Since then, he had daily urinary incontinence which increased over the weeks to several times daily. Immediately prior to admission, he had 5 days of decreased energy, oral intake and headaches. The patient was previously healthy with no significant medical history. On examination, the patient was febrile, but alert, active and able to move all extremities equally. Non-tender, non-mobile nodules were noted on the right frontal and parietal areas. His cranial nerves 2–12 were intact. He had no ataxia but had slight stumbling with walking quickly. Muscle strength in the bilateral lower and upper extremities were 5/5. Knee reflexes were mildly hyper-reflexic. No clonus was elicited and he described mild numbness, but normal sensation, in the left inner thigh area as well as around the testicles.

Laboratory evaluation showed a WBC count of $51 \times 10^9/L$ with haemoglobin of 113 g/L and platelets of $130 \times 10^9/L$. The WBC differential showed 26% segmented neutrophils, 18% bands, 4% lymphocytes, 2% atypical lymphocytes, 13% metamyelocytes, 3% myelocytes, 4% promyelocytes and 30% blasts. MRI of the brain and spine showed diffuse marrow infiltration of the calvarium, facial bones, clivus and cervical spine as well as an epidural mass measuring 2.1 cm compressing the posterior third of the superior sagittal sinus (figure 1). Extra-calvarial masses were also noted on the brain MRI consistent with the nodules noted on the physical

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Figure 1 Axial T1-weighted MRI of brain at diagnosis showing right extra-calvarial and sagittal sinus chloromas at the time of diagnosis (red arrows).

examination. MRI of the spine showed an epidural infiltrative soft tissue mass that filled the distal spinal canal from the level of L5-S1 inferiorly with extension into and filling of bilateral L5-S1 and all imaged sacral neural foramina as well as mild thickening and enhancement of distal cauda equina nerve roots (figure 2). The imaging characteristics of the mass were suggestive of a chloroma (isointense on T1-weighted MR images, hyperintense on T2-weighted MR images and enhancing with contrast). Chest X-ray was normal.

INVESTIGATIONS

Due to the presentation concerning for leukaemia, a bone marrow aspiration with biopsy and lumbar puncture were performed. The bone marrow evaluation showed a hypercellular marrow with 22% myeloid blasts with fluorescence in situ hybridization (FISH) testing positive for the t(8;21) ETO/AML1 fusion. The diagnostic lumbar puncture produced a normal cerebrospinal fluid (CSF) WBC count of 2/mm³ with a cytological examination positive for leukaemic blasts. Due to the chloromas of the sacral canal and symptoms of sacral nerve root compression, he was considered to have CNS disease, despite his having a normal CSF WBC count.

TREATMENT

The patient received intensive AML multi-agent chemotherapy on a St. Jude's Children's Research Hospital Consortium protocol. Due to the presence of the CNS disease and sacral

Figure 2 Sagittal T2-weighted MRI spine L5-S1 showing sacral involvement (red arrow).

nerve root compression, he received four lumbar punctures, with intrathecal chemotherapy given for the first two lumbar punctures, over the first 4 weeks of treatment. The first two lumbar punctures demonstrated a normal CSF WBC count and a small number of blasts, but all his subsequent lumbar punctures for the remainder of treatment demonstrated a normal CSF WBC count and no blasts. Shortly after receiving his day 1 intrathecal chemotherapy, he developed faecal incontinence in addition to his pre-existing urinary incontinence. This was attributed to further inflammation of the sacral nerves from his intrathecal treatment. His persistent urinary and faecal incontinence resulted in his having a long-term Foley placed, after which the faecal incontinence improved, presumably due to decreased urinary retention and a slow recovery of his sacral nerve root function. MRI of the spine after 1 week of treatment showed interval decrease in the tumour burden in the caudal spinal canal. The patient was in remission in the bone marrow on day 22 and considered low risk, due to the favourable cytogenetic characteristics, t(8;21) ETO/AML1 fusion and negative bone marrow minimal residual disease (MRD). FLT3 testing was negative. His extracranial masses had resolved and were no longer palpable. MRI of the spine showed a variable response to treatment with improvement in some areas and stable disease in others, including the sacral canal.

His second cycle of chemotherapy was started and his urinary incontinence slowly improved. He recovered some ability to feel the need to void and was discharged home on a schedule of clean intermittent catheterisation. After recovery from his third course of chemotherapy, he was able to void without catheterisation and without episodes of incontinence.

Four weeks into his fourth and final planned cycle of chemotherapy, he developed urinary and faecal incontinence again. MRI of the spine showed residual abnormal enhancing epidural soft tissue along the sacral spinal canal between the mid S1 and superior S4 levels, likely reflecting residual refractory disease (figure 3). This mass was moderately to significantly smaller in size than it was at the time of imaging at the end of induction 1, but its continued presence and enhancement with contrast and the new onset of incontinence was concerning for recurrent, refractory chloromatous disease with sacral nerve involvement. MRI of the brain and spine showed no evidence of residual extra-calvarial masses or epidural mass. Bone marrow aspiration and biopsy showed no evidence of bone marrow relapse.

Figure 3 Sagittal T1-weighted MRI sacral spine showing evidence of residual disease midline between S1 and S4 (red arrow).

OUTCOME AND FOLLOW-UP

Given the strong concern for sacral chloromatous relapse with sacral nerve involvement, high-dose corticosteroids were initiated and emergent radiation was commenced. After radiotherapy, his bladder and bowel function greatly improved. Repeat bone marrow aspiration continued to show no evidence of marrow disease, even with minimal residual disease testing. He was treated with reinduction chemotherapy with MRI of the sacral canal lesions showing stable disease after count recovery. He then proceeded to allogeneic stem cell transplantation to consolidate therapy. He had an MRI of the sacrum done approximately 4 months after stem cell transplantation which showed essentially stable mass size and enhancement. He remains in remission at the time of manuscript submission, 7 months after haematopoietic stem cell transplantation with chronic symptoms of a neurogenic bladder with urinary retention and overflow incontinence.

DISCUSSION

AML can present with chloromas or develop them at relapse. One such hypothesis for their development includes the myeloblast's propensity to home to specific areas of densely populated adhesion molecules that express certain proteins such as CD56.^{8,9} Chloromas can occur in the absence of bone marrow involvement and can be seen anywhere in the body, most commonly in the soft tissues, orbit, small intestine and around the CNS. Even if there is no detectable haematological involvement, it is thought that these cells originated in the bone marrow. Chloromatous presentation without haematological involvement has been shown to precede the diagnosis of bone marrow involvement by 10–11 months in up to 88% of patients.⁷ The (8;21) translocation has also been associated with presentation with chloromas and is more frequently seen with AML FAB M2, M5 and even M4 subtypes of differentiation.^{7,8,10}

Spinal cord involvement is rare and is found in approximately 3%–9% of cases with chloromatous involvement.^{3,4,7,8,11} All spinal levels may be affected; however, the thoracic region is the most common location, followed by the lumbar, sacrum and cervical spinal cord. The sacral spinal cord is involved 23% of the time and 18% of patients with spinal involvement have multiple lesions.⁷ There are reports of relapses of chloromas, including in a 23-year-old patient with an S2-level chloroma who achieved complete remission (CR) after reinduction for recurrent disease.¹⁰ The patient received total body irradiation as well as reinduction followed by allogeneic haematopoietic stem cell transplant (HSCT).

Systemic, intensive chemotherapy has been shown to be the most effective mode of treatment of chloromas, including those involving the CNS.^{5–7} Radiation therapy may be used in the treatment as well, and has shown to be extremely effective. A treatment regimen of 24 Gy in 12 fractions was an appropriate regimen with excellent disease control and palliation without significant toxicity.¹² It is generally preferred to refrain from surgery because of the positive responses to chemotherapy and radiation therapy. Radiation therapy after relapse or persistence of disease may be an important aspect of treatment if not used as initial treatment.

HSCT is an important treatment regimen with the potentially additional benefit of graft versus leukaemia effect.^{11,13,14} Effector CD8+ T cells has been shown to be an important aspect of this phenomenon, mainly in the comparison of allogeneic HSCT as compared with syngeneic and T cell-depleted HSCT.^{8,13,14}

As this patient had several chloromas that responded to chemotherapy, persistence of his sacral canal lesions suggests that this may be a sanctuary site for AML. Persistent residual disease in AML has been a major concern with many studies showing that 10%–40% of AML cases do not achieve CR.⁶

Given this patient's course, future studies would be needed to investigate whether the sacral canal area serves as a sanctuary site, and whether residual, but shrinking, lesions on imaging are predictive of relapse in the absence of bone marrow disease or CSF disease by lumbar puncture.

Learning points

- ▶ Acute myelogenous leukaemia (AML) subtypes M2, M4 and M5 are more likely to have chloromatous involvement.
- ▶ Different chloromatous sites may have different responses to chemotherapy.
- ▶ Imaging may be required to follow chloromatous disease in AML, even if the bone marrow disease and cerebrospinal fluid responds completely to chemotherapy.
- ▶ Radiation therapy may be required for persistent chloromatous disease in sanctuary sites.
- ▶ Sacral chloromas of the spinal canal may be a specialised sanctuary site for AML.

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