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Spinal cord disease in children with malignancies: Clinical cases and literature review

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Spinal cord disease in children with known or suspected malignancy is an oncological emergency because it commonly implies malignant spinal cord compression (SCC). Since the outcome of SCC is primarily determined by the patient's neurological status at treatment initiation, the goal must be to establish the underlying diagnosis before development of irreversible spinal cord damage. A high index of suspicion is key to early diagnosis; it is therefore mandatory that all health care workers involved in the care of children should have a basic acquaintance with this potentially catastrophic condition. Four cases of children with malignancies and spinal cord pathology are presented. Current knowledge of this condition is reviewed.

Case presentations

Case 1

A 32-month-old boy presented to a remote primary health care clinic with a 20-month history of progressive lower limb dysfunction. He had attained his early developmental milestones as expected, but at 12 months of age he had lost the ability to walk. This was followed by refusal to stand and eventually inability to move his lower limbs. Bowel and bladder control had never been attained. He had no significant previous medical history and there had been no traumatic incidents.

Examination revealed profound symmetrical weakness, increased tone and sustained clonus in both legs. There was an extensor plantar response on the left. The upper limbs were normal. Localised spinal tenderness or a sensory level could not be demonstrated and the bladder was not palpable.

The patient was referred to Universitas Hospital, where emergency magnetic resonance imaging (MRI) revealed a mid-thoracic paravertebral mass with infiltration via the intervertebral foraminae. There was no obvious epidural invasion, but the spinal cord (SC) appeared atrophic and thin in the mid-thoracic region (Figs 1 and 2).

Dexamethasone was not initiated. Given the protracted course and the established SC atrophy, it would be unlikely to have had any beneficial effect. A computed tomography (CT)-guided biopsy was done and the histological features were suggestive of a ganglioneuroblastoma. After appropriate staging investigations excluded distant metastases, chemotherapy was commenced. The neurological features remained unchanged and a follow-up MRI done after 6 cycles of chemotherapy showed little shrinkage of the tumour. The tumour was resected, followed by an additional 3 cycles of chemotherapy. The patient remains in remission, but the paraplegia is considered to be permanent.

Case 2

A 29-month-old girl was referred to a plastic surgery unit with a 4-month history of a progressively enlarging nasal tumour. Debulking of the lesion was done and the histological features were compatible with an embryonal rhabdomyosarcoma. She was subsequently referred to the paediatric oncology unit, where appropriate staging investigations confirmed that the tumour was confined to the nasal soft tissue.

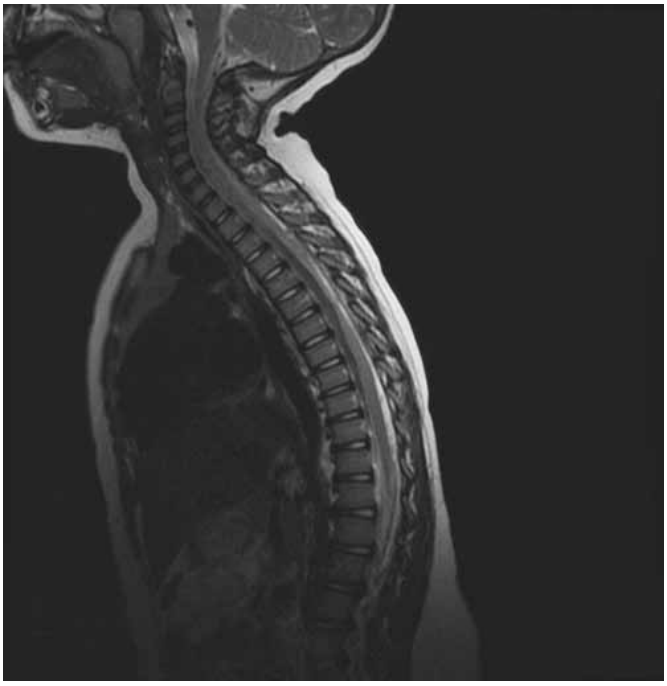

Fig. 1. Sagittal view: atrophy of the spinal cord in the mid-thoracic region, caused by longstanding cord compression.

Appropriate chemotherapy was initiated and a satisfactory clinical response was noted, but after 15 weeks of chemotherapy (with 36 weeks to go before completion) the patient failed to return for her appointment. She presented 4 months later with a fungating mass protruding through both nostrils, causing complete nasal obstruction, proptosis of the right eye, profound cervical lymphadenopathy and a 4 cm hepatomegaly. The cranial nerves were intact and the upper limbs normal, but she had flaccid paralysis involving the lower limbs, clonus in both ankles and bilateral extensor plantar responses. She had been wearing nappies since birth and there was no history of constipation.

Dexamethasone was started at a dose of 1 mg/kg/d for suspected paravertebral peritumoural oedema. An urgent MRI scan showed

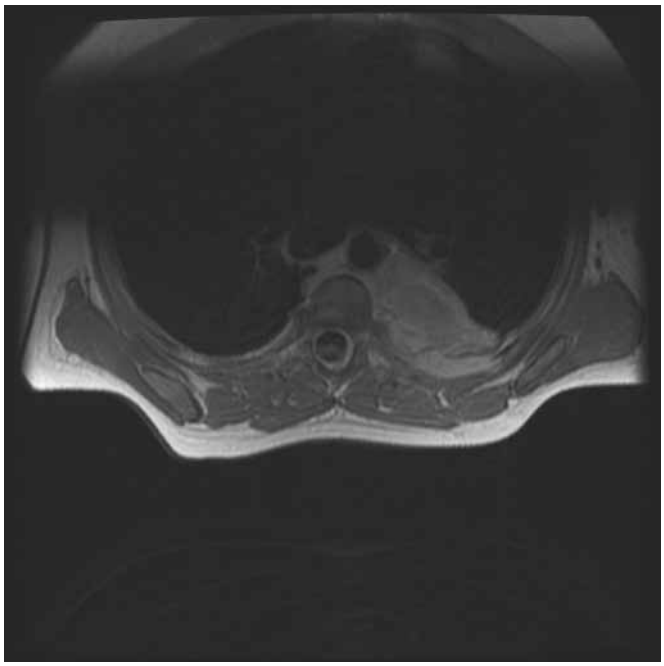

Fig. 2. Coronal view: Paravertebral tumour extending through the intervertebral foramina.

an increased signal in the T2 vertebral body with post-contrast enhancement, but no SC indentation or paraspinal soft-tissue masses. A skeletal isotope scan confirmed disseminated skeletal metastases involving the maxilla, skull, thoracic vertebrae, right ileum and left femur. There was also evidence of bone marrow infiltration.

The patient is currently on palliative treatment with second-line chemotherapy and has shown significant improvement to the extent of having regained ambulation. However, the prognosis for long-term survival with a metastatic rhabdomyosarcoma is poor.

Case 3

A 36-month-old girl presented to a paediatric practice with a month's history of jaundice and pale stools. On examination she had generalised lymphadenopathy, hepatomegaly and a central lobulated abdominal mass. Blood biochemical analysis revealed conjugated hyperbilirubinaemia, hypoalbuminaemia, raised liver transaminases and ductal enzymes, and anaemia of chronic disease.

She was referred to the Paediatric Oncology Unit at Universitas Hospital, where an abdominal CT scan showed the abdominal mass to be a large conglomerate of lymph nodes, stretching from the porta hepatis inferiorly and causing displacement of the liver laterally. Further staging investigations excluded pulmonary lesions and bone marrow involvement. It was, however, confirmed that she was HIV infected.

An open biopsy was done and, since the CSF analysis failed to demonstrate malignant involvement, the diagnosis of stage III abdominal Burkitt's lymphoma in an immunocompromised child was made. She was started on antiretroviral medication. In order to avoid profound tumour lysis, chemotherapy was commenced with two initial reductive phases, including a dose of intrathecal methotrexate and hydrocortisone in each. This was followed by an induction phase consisting of multiple-drug, high-dose systemic as well as intrathecal chemotherapy. The clinical response was satisfactory, and after haematological recovery the patient was discharged on her antiretroviral drugs. She had a follow-up date for the second cycle of chemotherapy, but because of unfortunate social circumstances she failed to return.

The patient presented 5 months later with a 3-month history of inability to walk as well as incontinence of urine and stools. On examination she was irritable with cervical and axillary lymphadenopathy. The abdominal mass had disappeared, but she had a spastic paraparesis with flexion contractures of the feet. The CD4 percentage of lymphocytes was only 6.9%, raising questions about antiretroviral compliance and resistant virological strains.

A repeat abdominal CT scan revealed only 2 lymph nodes measuring 2×3 cm in the region of the original mass. These were biopsied and the histological features were compatible with HIV-associated lymphadenopathy as well as tumour necrosis. No viable tumour could be detected. The bone marrow was still clear of foreign cells, but showed myelodysplasia, as is seen with HIV infection.

An MRI scan to investigate the SC dysfunction was reported to be normal. Cytological examination of the CSF still failed to demonstrate malignant cells. Further special investigations included syphilis serology, an HTLV 1 and 2 antibody screen, determination of CSF adenosine deaminase (ADA) activity, measurement of the red cell folate level and serum vitamin B_{12} level, and a CT scan of the brain. None of these demonstrated an underlying cause for the neurological deficit. The final diagnosis of HIV myelopathy was made in consultation with a paediatric neurologist.

Since the cancer was histologically confirmed to be in remission, no further chemotherapy was deemed necessary. The social circumstances were addressed and the importance of antiretroviral compliance was emphasised. Two years later, the patient remains in remission and has shown good virological and immunological response to her antiretroviral treatment, but the neurological picture remains unchanged.

Case 4

An 11-year-old girl presented with unilateral leukocoria. A CT scan of the brain revealed calcification involving the retina and posterior chamber of the left eyeball. The eye was enucleated and histological examination confirmed a retinoblastoma with infiltration of the optic nerve to the surgical margin. Cytological analysis of the CSF detected no malignant cells, and the bone marrow was also clear of foreign infiltrates.

The patient was treated with 6 cycles of systemic and intrathecal chemotherapy as well as orbital and craniospinal irradiation. The response was satisfactory with the achievement of clinical and radiological remission.

During a long-term follow-up visit 22 months after completion of the first-line chemotherapy, she presented with obtundation and dehydration. A CT scan showed multiple nodular meningeal lesions with early hydrocephalus, a picture consistent with a meningeal relapse. She received palliative treatment with an additional 30 Gy of cranial irradiation.

Three months later the clinical picture worsened dramatically with the onset of symmetrical weakness involving all the limbs, but affecting the legs more than the arms. She also developed urinary incontinence. An MRI scan of the spine confirmed widespread drop metastases affecting most of the SC below the level of C3/4. Treatment with dexamethasone was initiated and the spine irradiated to a total dose of 20 Gy. These palliative modalities succeeded in relieving her pain. However, she developed an infected pressure sore and died within 6 months of the relapse.

Discussion

The above cases represent four different scenarios of SC disease in children with malignancies. In case 1, the neurological deficit was the first manifestation of a primary paravertebral tumour. In the second case, the primary tumour was in the nasal region and later metastasised to the thoracic vertebrae, causing spinal cord compression (SCC). The third case illustrates SC pathology unrelated to the malignancy and caused by a co-morbid condition. In the last case, SC disease

was secondary to relapse of a malignancy that had clinically been in complete remission. These cases illustrate that SC pathology can occur at any point in the evolution of an oncological disease. Clinicians involved in the care of these patients must maintain a high index of suspicion at all times. It is crucial to recognise malignant SCC, but the non-neoplastic causes of neurological deficits must also be kept in mind. These include chemotherapy-related myelitis, radiation myelopathy, transverse myelitis, infective processes (e.g. tuberculosis and HIV), acute demyelinating conditions and SC stroke.[1]

The spectrum of paravertebral tumours seen in paediatric patients may cause epidural SCC through a stepwise process. Infiltration of the epidural space takes place through the intervertebral foraminae, leading to compression of the thecal sac. Any degree of indentation of the thecal sac on MR images may be considered evidence of epidural SCC. As the tumour grows in the epidural space, it generally takes the path of least resistance and encircles the thecal sac. The resultant obstruction of the epidural venous plexus leads to vasogenic oedema of the spinal cord. Left unattended, the cord will become ischaemic and infarcted and, as illustrated by the atrophic cord in case 1, the neurological damage will be irreversible. SCC may also be caused by metastatic spread to the cord parenchyma.[2] Examples include drop metastases from an intra-cranial tumour such as an ependymoma or retinoblastoma.

Of 1 405 children treated at the Universitas Paediatric Oncology unit between 1995 and 2010, 36 (2.5%) either presented with or developed spine or spinal cord involvement. Neuroblastomas, relapsed retinoblastomas and metastases from non-Hodgkin's lymphomas were most commonly implicated. Even though malignancies involving the spine or spinal cord are not common as primary or secondary tumours, they account for a disproportionate degree of morbidity.[2] Remission may be achieved, but neglected neurological deficits almost always result in permanent disability.

SC disease is usually diagnosed late in the evolution of the pathological process. A review of the literature revealed the following contributing factors:

1. The clinical features of SC disease with which most clinicians are familiar include back pain, localised spinal tenderness, motor deficits (weakness/spasticity at or below the level of the lesion), sensory abnormalities and sphincter disturbances. However, these widely recognised features of cord pathology occur late in the natural history of the disease process. The clinical features of early cord involvement are less well defined. This is especially true of paediatric patients. Early symptoms may fluctuate in intensity and the findings on neurological examination may even be normal in the presence of a spine or spinal cord tumour.[3,4]

2. Even the established features of spinal cord pathology can be subtle in children. Young children may be unable to communicate the fact that pain is present. They are even less able to localise the pain, and may complain of abdominal pain or headache rather than back pain. Young children often refuse to walk when ill, and parents may easily miss true limb weakness. Clinicians who are not familiar with the normal motor development of a child may fail to recognise motor milestone regression.[3]

3. Sphincter disturbances, usually constipation and urinary retention with overflow incontinence, are a relatively uncommon presentation in children. Sensory deficits are also rare, and even when present may in the best of circumstances be difficult to detect in young children.[3,4]

4. It has been reported that symptoms in patients with cancer differ in significance from the same symptoms in the general patient population without cancer.[5] In a child known to have had cancer, progressive and/or severe pain should ideally be managed as cancer recurrence or progression until proven otherwise.

5. In the case of possible malignant SCC (i.e. excluding spinal injuries), time should not be wasted arranging plain radiographs or isotope scans. Pollono *et al.*[6] reported simple radiographic studies to be positive in only 49% of a group of 68 paediatric patients with malignant SCC. MRI is the only modality that provides adequate imaging of the SC, and it should be the investigation of choice in the case of suspected malignant SCC.[7] Urgent referral may be necessary to obtain an MRI scan. A CT scan does not demonstrate the SC or epidural space clearly, but it is superior to MRI for imaging of bony abnormalities and may be of value when MRI is not an option.

6. Optimal management of SCC requires a multidisciplinary team effort in an urgent setting. Input is required from at least the referring physician, paediatric oncologist, neurosurgeon, radiologist and radiation oncologist, among others. Lack of co-ordination and communication between the involved disciplines may lead to unacceptable diagnostic and treatment delays.[8] The patient should primarily be referred to a paediatric oncologist, who will then co-ordinate the multidisciplinary approach.

In our experience, traditional and socio-economic barriers also contribute to presentation with advanced disease. Inhabitants of remote settings may find it difficult to access medical centres, and caregivers may opt for traditional remedies before seeking medical care. Current caregivers may be unaware of the child's previous medical history, leading to poor treatment compliance. Even though initially informed, caregivers often still fail to realise the devastating consequences of treatment interruption. It seems that education of caregivers and families is not only a weak link in under-privileged communities. With regard to malignant SCC in adult patients in a First-World setting, Abrahm[9] stated that 'Further research is needed to develop and validate educational approaches that will alert but not alarm patients and their families, and will heighten the index of suspicion of oncologists, primary care, and ER physicians for epidural disease.'

An important issue to be considered in the management of malignant SCC is the use of dexamethasone. It produces a reduction in vasogenic cord oedema that often significantly improves the neurological features. However, dexamethasone is not an alternative to definitive SC decompression. It only serves to rescue the cord compression until the multidisciplinary team has decided on the optimal decompressive strategy for the specific patient. This may be urgent decompressive surgery, chemotherapy or radiotherapy. The appropriate dosage of dexamethasone for malignant SCC in children is controversial. A loading dose of 1.0 - 2.0 mg/kg followed by 0.25 - 0.5 mg/kg every 6 hours has been suggested.[1,2] It must be kept in mind that leukaemia and lymphoma cells are extremely sensitive to corticosteroids. Dexamethasone may induce tumour lysis, and the histological picture may be altered to such an extent that confirmation of the diagnosis becomes impossible after only 48 - 72 hours.[3,4] Steroids should preferably only be started under specialist supervision.

Conclusion

Malignant SCC is the most ominous cause of SC disease in paediatric oncology patients, but it may also be caused by a non-neoplastic co-morbid condition. Neglected cases may result in frank paralysis. The reasons for delay in presentation, diagnosis and management are multiple and varied. Weak links may exist at the level of the patient, the family, the health system and the treatment team. Early dexamethasone may rescue SCC, but should be discussed with a specialist before initiation.

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