Reminder of important clinical lesson

Bee-sting, a non-resolving wound and a progressive mass over the right eye preceding the ultimate diagnosis of frontal bone Ewing's sarcoma

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Summary

A healthy young lady suffered a bee-sting over her right eyelid which was followed by pain, redness and swelling at, above and beyond the right eyelid. Although the initial swelling subsided, the patient noticed a small 'lump', superior to the eyelid which persisted after the rest of the swelling disappeared. This lump subsequently progressed over a span of 3 months and then caused ulceration of the overlying skin. Further testing revealed the lump to be an Ewing's sarcoma arising from the frontal bone. The patient was treated with standard chemotherapy (16 cycles of vincristine, doxorubicin, cyclophosphamide alternating with cycles of ifosfamide and etoposide) and radiotherapy and has remained disease-free 18-months after completion of treatment. This report reminds the reader about a not-so-uncommon mode of presentation of malignancies, that is, they being discovered after attention drawn by a rather common injury or trauma.

BACKGROUND

It is not uncommon for inflammation to develop after insect bites. In the patient under current discussion, the resolution of inflammation directed attention towards a residual non-resolving mass. However, when the mass progressed rapidly and went on to become painful and caused a breach in the overlying skin, subsequent imaging and histopathology revealed the nature of the 'small lump which quickly progressed' to be an Ewing's sarcoma arising from the frontal bone. The patient did enjoy a complete response to treatment, and remains disease-free for 18 months after completion of treatment. This case offers an important reminder that many malignancies are detected after attention has been directed towards the site by a rather unrelatable cause.

CASE PRESENTATION

A young lady had a history of a bee sting over the right eyelid which was followed by acute pain and swelling. Over a span of a week, the symptoms largely subsided after treatment with anti-inflammatory and antihistaminic drugs. However, a 'small residual swelling' supposedly failed to subside and, in the patient's words, continued to enlarge in size over a span of 3 months (figure 1). When the swelling suddenly got enlarged and caused ulceration of the overlying skin, the patient reported to her physician, who noted granular solid extrusions admixed in pus. After initiating appropriate antibiotics, the 'solid-extrusions' were sent for histopathological analysis.

INVESTIGATIONS

Examination of the material with haematoxylin-eosin staining revealed a 'small-round blue cell tumour' (figure 2). Further, MRI (figure 3) and a bone scan (figure 4) revealed

Figure 1 A swelling over and above the right eye displaying redness and a dried-up ulcer.

Figure 2 'Small round blue cells' visualised on haematoxylin-eosin staining.

the origin to be from the frontal bone. The diagnosis was finalised as 'Ewing's sarcoma', since further testing showed positivity for CD99 and negativity for neuron-specific enolase (NSE).¹

TREATMENT

Neo-adjuvant chemotherapy based on standard-dose² vincristine, doxorubicin and cyclophosphamide/ifosfamide and etoposide (VDC/IE) regimen (cycles of vincristine, doxorubicin and cyclophosphamide; alternating with cycles of ifosfamide and etoposide) was initiated, and a considerable resolution of the tumour was seen even after a single cycle (figure 5). Chemotherapy was continued for a total of 16 cycles. Further, intensity-modulated radiation therapy (IMRT) was also incorporated into treatment, and 54 Gray (Gy), at 1.8 Gy per fraction, was delivered to the site of initial tumour.³

Figure 3 MRI revealing a mass lesion arising from the inferior aspect of the frontal bone.

Figure 4 Bone-scan demonstrating a focus of intense tracer-uptake over the right frontal bone. It is to be noted that the bone-scan exaggerates the linear extent of the tumour because of reactionary uptake of tracer in the surrounding bone.

Figure 5 Remarkable regression after the first cycle (the *first* of 16 cycles) of chemotherapy.

OUTCOME AND FOLLOW-UP

As on the date of this writing, the patient has remained disease-free for 18-months post-treatment. There have been no complications such as cerebrospinal fluid leak, or frontal bone defects either.

DISCUSSION

Ewing's sarcoma is mostly a disease affecting children in the pubertal age group, who make up approximately 40–50% of the cases. However, 25–30% of cases occur in prepubertal children and approximately 5% of cases occur in adults.⁴

Majority of the cases involve long-tubular bones, pelvis, spine and ribs (together constituting around 80% of all cases). Primary Ewing's sarcoma arising from the skull is rare, with various case-series indicating that only approximately 1–3% of all cases arise from the skull. In fact, the jaw is a more common site of origin of Ewing's sarcoma when compared with the skull.^{5–7} Further, a series of 33 cases of Ewing's sarcoma of the skull comprised of 18 cases arising from the calvarium, with the remaining cases arising from the skull base.⁸

Ewing's sarcoma has a neuro-ectodermal origin and hence, is not a 'sarcoma' in the true sense. Histologically, it is considered as one of the 'small-round-blue-cell' tumours, given its microscopic appearance on a classical haematoxylin-eosin stain. Individual cells show a lack of organelles and often contain abundant glycogen, and hence are periodic-acid schiff (PAS) positive. Ewing's sarcoma indeed is the least differentiated in the spectrum of primitive neuro-ectodermal tumours (PNET), while the most-differentiated form would be an entity named 'primitive neuroepithelioma'.¹

Ewing's sarcoma can be differentiated from other small-round-blue-cell tumours (such as neuroblastoma and rhabdomyosarcoma) with the use of a set of histopathological features and immunocytochemistry. Ewing's sarcoma is invariably PAS positive and CD99 positive (however, this may be occasionally positive in other small-round-blue-cell tumours too). With Ewing's

sarcoma, there is a characteristic absence of neuro-secretory granules (a feature invariably seen in neuroblastoma, and also occasionally seen in rhabdomyosarcoma). There is a sparse presence of organelles in Ewing's sarcoma (whereas a variable amount of organelles are seen in rhabdomyosarcomas and neuroblastomas).^{1 9}

Ewing's sarcoma is negative for further markers that may be positive in the other small-round-blue-cell tumours (eg, muscle-specific actin, desmin, S-100, chromogranin and synaptophysin). In addition, Ewing's sarcoma is mostly (but not invariably) negative for NSE. On cytogenetic analysis, the presence of the t(11;22), t(21;22) or t(7;22) translocations are specific for PNETs including the Ewing's sarcoma. Whereas translocations such as t(2;13) can be expected in rhabdomyosarcomas.^{1 9}

The rapid progression to cause pain is a common feature with Ewing's sarcoma. Although there is no universally accepted staging system for Ewing's sarcoma, certain factors identified to be of poor prognostic significance are metastatic disease at presentation (the most important prognostic factor), bone marrow involvement, high pretreatment serum lactate-dehydrogenase, primary Ewing's sarcoma of the rib (Askin's tumour), older age, tumour size more than 200 cc and soft-tissue extension. Tumour site is another recognised prognostic factor, with distal extremity tumours having better prognosis. Another prognostic factor recently identified is the 'response to neo-adjuvant chemotherapy'.^{10–14}

The patient under current discussion had a very good response to neo-adjuvant chemotherapy, and there was a complete remission of disease after the fourth cycle. Given the established optimum duration of chemotherapy as 49 weeks, with chemotherapy administered once every 3 weeks, our patient received a total of 16 cycles of chemotherapy. The regimen chosen in our institute comprises alternating cycles of VDC and IE, given every 3 weeks with granulocyte colony-stimulating factor (G-CSF) support.^{2 15}

The 'standard-of-care' with chemotherapy with Ewing's sarcoma, or any paediatric malignancy for that matter, has remained to be a 'work-in-progress', with various multinational trials underway. With regard to the

choice of chemotherapy, the other options would be the addition of D-actinomycin to VDC, or to substitute cyclophosphamide with ifosfamide. There has been evidence of improvement with the use of 'dose-dense' chemotherapy, that is, the delivery of chemotherapy every twice weekly, rather than thrice weekly.¹⁶ Also, there have been efforts to reduce the overall span of chemotherapy to approximately 25–30 weeks.¹⁷

After completion of chemotherapy, the patient in discussion received radiotherapy with IMRT to a dose of 54 Gy delivered in 30 fractions of 1.8 Gy each. Radiotherapy was targeted to the small volume of frontal bone which was initially involved by tumour (prechemotherapy volume). Radiation dose limits to critical organs such as the lens, retina and brain were below recommended limits.

The standard of care in Ewing's sarcoma includes 'local-treatment' after systemic neo-adjuvant chemotherapy. Local treatment may include surgery, or radiotherapy, or at times, both. Surgical option was not contemplated given the complete response after neo-adjuvant chemotherapy. It is indeed a proven fact that the response to neo-adjuvant chemotherapy is in itself a prognostic factor.¹⁸

As of the date of this writing, the patient has completed 18 months of post-treatment follow-up and has remained free of disease. We remind the reading clinician that an occasional malignancy may be unmasked by a patient presenting with a rather 'unrelatable' condition. Other similar situations would be the detection of solitary pulmonary nodules on chest-radiographs, the detection of abdominal 'incidentalomas' on imaging for trauma, or the detection of bone tumours after attention generated from trivial trauma.^{19 20}

Learning points

- During routine clinical practice, one mode of presentation of malignancies is their 'discovery' after being unmasked after common events such as trauma.
- Ewing's sarcoma when non-metastatic can be offered high chances of cure after neo-adjuvant chemotherapy prior to local therapy with surgery or radiotherapy.
- Modern radiotherapy techniques such as intensity modulated radiation therapy allow the delivery of radiotherapy with minimal radiation doses to surrounding critical structures.

Competing interests None.

Patient consent Obtained.

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