On-line Case Report

Very late local recurrence of Ewing's sarcoma – can you ever say 'cured'?

A report of two cases and literature review

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ABSTRACT

We report two rare cases of very late local recurrence of Ewing's sarcoma, occurring 16 years and 19 years after treatment of the primary tumour. In both cases, disease remission had been achieved. Both patients originally underwent non-surgical combined modality therapy following initial diagnosis and both were rendered disease-free. After a long latent phase, both started experiencing unexplained local symptoms. These were investigated at their local hospital but tumour recurrence was not initially considered as a cause of these symptoms. The two patients were eventually referred back to our institution after the diagnosis of recurrent Ewing's sarcoma was established. Both have successfully undergone complete excision of the recurrences and are receiving postoperative adjuvant therapy. These cases highlight the need to remain vigilant for local recurrence, however long after the initial diagnosis.

Keywords: Ewing's sarcoma – Local recurrence – Combined modality therapy – Remission – Prognosis

The prognosis of the biologically enigmatic Ewing's sarcoma family of tumours (ESFT) or primitive neuro-ectodermal tumours (PNET) has dramatically improved since the development of modern chemotherapy. Prior to the era of systemic treatment, over 90% of patients died from systemic, pulmonary, and/or multiple bone metastases within 2–5 years.¹ However, this has now changed and it has been repeatedly demonstrated that these can be essentially curable cancers.^{1–3}

The chance of cure will depend on a variety of factors – the presence of metastases, the size of the tumour, anatomical location, general health of the patient and other individual factors. Also important is how the disease responds to treatment; how much of the main

tumour bulk can be removed/destroyed by surgery and/or radiotherapy, and the number of cancer cells responding to chemotherapy.

Current protocols include a combination of systemic treatment (intensive combinations of multicycle chemotherapy) and local treatment (surgery and/or radiotherapy). Problems related to the effectiveness of radiotherapy in controlling the primary lesion and to late side effects and complications have made it necessary to reconsider the role of surgery in the treatment of primary disease.^{1–3}

Current studies show that, following achieving remission in patients with non-metastatic Ewing's sarcoma, 30–40% of these patients will still develop recurrent disease (local and/or metastases) at some

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Figure 1 MRI showing recurrent disease in the distal fibula.

point.¹ Most studies in the literature on the long-term outcome of non-metastatic Ewing's sarcoma report a time range of 2–10 years between commencing treatment and development of local recurrence.^{4–6}

Case report 1

A 54-year-old Caucasian woman presented to her local hospital with a history of an enlarging painful mass in her left ankle in 1986. Plain radiographs at the time suggested the diagnosis of a bone tumour affecting the distal fibula. Imaging was carried out at the local sarcoma unit, including an MRI of the left lower limb and CT scans of the chest, abdomen and pelvis. These revealed a suspicious lesion affecting the distal fibula with no distant metastases. A subsequent needle biopsy confirmed the diagnosis of Ewing's sarcoma. Based on these findings, VAC chemotherapy (vincristine, adriamycin, cyclophosphamide) and radiotherapy (60 Gy) were administered in late 1986. Good symptomatic recovery was achieved and a needle biopsy revealed excellent response to chemotherapy (> 95% necrosis). The patient was followed up on a 6-monthly basis for 2 years, and then on an annual basis between 1988 and 1997. A plain radiograph of the chest and distal tibia were obtained before each clinic appointment. As the patient was disease-free for 10 years, she was discharged to the care of her general practitioner.

In 2005, 19 years after the initial diagnosis, the patient suddenly developed pain and redness in her left ankle with no history of trauma. As her inflammatory markers were raised, this was presumed to be an infective process and she was treated at her local hospital with antibiotics

Figure 2 Pelvic radiograph following subtotal sacrectomy for recurrent Ewing's sarcoma.

for 2 months. Because no improvement resulted from the above treatment, she was referred to her local sarcoma department. An MRI of the left ankle demonstrated a lytic lesion in the distal fibula with no soft tissue component. No distant metastases were detected. A needle biopsy confirmed the diagnosis of recurrent Ewing's sarcoma. Six cycles of VIDE chemotherapy (vincristine, ifosfamide, doxorubicin, etoposide) were administered in 2005–2006, but significant residual tumour volume was still present post therapy.

At this stage, this patient was referred to our institution for a possible limb salvage procedure. A left distal fibula resection was performed in September 2006. Histopathology examination confirmed the complete excision of a recurrent Ewing's sarcoma with good response to pre-operative chemotherapy (> 90% necrosis). She remains well.

Case report 2

A 39-year-old Caucasian man presented to his local hospital with a history of alteration in bowel habits in early 1990. MRI revealed a mass arising from the sacrum, and a needle biopsy was in keeping with Ewing's sarcoma. There were no distant metastases. Based on these findings, IVAD chemotherapy (ifosfamide, vincristine, adriamycin, actinomycin D) and radiotherapy (55 Gy) were administered in 1990. This was supplemented with doxorubicin in 1991. Treatment was completed in June 1991, and a repeat needle biopsy revealed excellent response to chemotherapy (> 95% necrosis). The patient was followed up on an annual basis between 1991 and 2002 at a sarcoma unit and was completely asymptomatic. Chest X-rays were obtained in clinic on each occasion, but no sacral imaging was performed after 1993.

In March 2006, the patient started complaining of intermittent right buttock pain, general malaise and tiredness. No bladder or bowel symptoms were present. Further investigations demonstrated the presence of presacral mass encroaching into the right-sided exit foramina at S1 and S2, and multiple lung metastases. A general anaesthetic CT-guided biopsy confirmed the diagnosis of Ewing's sarcoma. VAC and IVAD chemotherapy was administered in 2006, following which the lung lesions improved dramatically, but significant sacral residual tumour was still present post therapy.

A subtotal sacrectomy with colostomy formation was performed at our institution in November 2006, and histopathology testing confirmed the diagnosis of a recurrent Ewing's sarcoma (complete excision) with poor response to pre-operative chemotherapy.

Further adjuvant therapy has been commenced postoperatively and close follow-up is planned.

Discussion

James Ewing, Professor of Pathology at Cornell University in New York, first described Ewing's sarcoma in 1920. This distinctive, small, round cell sarcoma is a highly malignant neoplasm representing the fourth most common bone tumour overall, but the second most common in children and adolescents, with an annual incidence of 0.6 per million of the population.^{7,8}

Most frequently, the tumour is diagnosed as a monostotic lesion in the metaphysis or diaphysis of long bones of the extremities. The tumour also may occur less frequently in the pelvis, ribs, or scapulae. Typically, the periosteal reaction creates an onion-skin appearance as new bone is deposited. The radiographic appearance can vary highly from a lytic appearance to sclerosis.

Survival rates have greatly improved since the introduction of modern chemotherapy. If the tumour is localised in one area and is surgically resectable, the 5-year survival rate can be as high as 75% when chemotherapy and radiotherapy are also administered. If, however, the tumour is large and cannot be resected, the 5-year survival rate is less than 50%, even after a good response to chemotherapy and radiotherapy. When metastatic disease is present at diagnosis, the 5-year survival rate is less than 25%.^{4,9}

Many studies have reported the pattern of local recurrence after disease remission and its relation to the prognostic factors^{2,4-6,10} and in the majority of these studies, tumour relapse (local recurrence and/or metastases) occurred between 2–10 years after starting initial treatment.⁴⁻⁶

Bacci *et al.*⁴ reported therapy and survival rates after recurrence of treated non-metastatic Ewing's sarcoma in

195 patients, the mean relapse time was 27.3 months with one patient developing local recurrence 222 months (18.5 years) after initial treatment. Of these recurrences, 51.7% occurred between 2–5 years.

Gasparini *et al.*¹⁰ described the long-term outcome in 121 patients with monostotic Ewing's sarcoma treated with combined modality therapy. The mean follow-up in this study was 12 years, with one patient developing local recurrence at 14 years.

No specific factors have been clearly linked to the variability in the length of the latent phase after achieving first remission in Ewing's sarcoma patients. This variability is present in all age groups and in both genders. However, as the method of local treatment (surgery and/or radiotherapy) has been reported to affect long-term outcome,¹⁰ this may also be related to the duration of the remission state.

Only a small number of studies have specifically examined survival after recurrence in Ewing's sarcoma. From these studies, factors associated with superior survival included: local recurrence only, lung metastases rather than extra-pulmonary disease, definitive surgery to the site of relapse, and relapse more than 2 years from diagnosis. Where stated, 5-year survival from these studies ranged from 13.8% to 20.0%.^{4,5,8,10}

Conclusions

Our cases demonstrate the possibility of very late (16 and 19 years) local recurrence of Ewing's sarcoma. In both patients, recurrent disease was not initially considered as an explanation of the new symptoms.

In the first case, the patient was treated with a lengthy course of antibiotics, as her disease mimicked an infective process. The good initial response to treatment resulted in a considerable delay in discovering her recurrent disease.

We conclude by emphasising two important points:

1. The need for life-long follow-up of Ewing's sarcoma patients at a specialist centre for bone and soft-tissue tumours. Further studies are required to assess the role of different imaging techniques in the long-term follow-up of these patients.
2. Recurrent disease should always be considered in patients presenting with any unexplained symptoms even after a long (> 15–20 years) disease-free interval.

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