CASE REPORT

Fifty-four-month survival in a 3-year-old child presenting with an aggressive metastatic dedifferentiated clival chordoma

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SUMMARY

Dedifferentiated chordoma is a rare, aggressive, chemoresistant and radioresistant malignancy arising from notochord remnants that can occur anywhere along the spine. Incidence in patients under 20 years of age is 1 per 250 million. We report a case of dedifferentiated clival chordoma presenting in a 3-year-old boy with pulmonary metastasis, which responded unusually well to chemotherapy, achieving complete metastatic clearance and debulking of the primary tumour. Proton beam therapy achieved further tumour control, with excellent quality of life for multiple years. On disease relapse, an atypical lateral transcondylar surgical approach achieved complete macroscopic clearance but there was cutaneous seeding. This, and continued primary site activity, failed to be controlled with targeted therapy, traditional chemotherapy and photon radiation, resulting in gradual neurological decline and death. Intensive management resulted in above-average survival despite diagnosis late in the disease course, which may be of value directing investigation into optimal management.

BACKGROUND

Chordoma is a rare, slow growing, chemoresistant and radioresistant locally aggressive malignancy that arises from notochord remnants. It usually presents in adults, with a median age of 49 years at diagnosis for skull-based chordomas. This case describes a rare aggressive dedifferentiated metastatic variant of the disease, presenting in a 3-year-old child. Similar cases are extremely limited (1 in 250 million incidence), making management decisions difficult when clinicians, patients and their parents face this disease. As such, case reports are of great value for determining patterns of presentation, response to interventions and identifying effective management strategies.

This adds a case to the increasing evidence that dedifferentiated chordoma in children tends to be much more chemo sensitive than slower growing versions. The prognosis was initially very bleak, with options of not initiating any treatment discussed due to the advanced stage of disease. The initially excellent response to treatment, and multiple years of high quality of life for the child, with minimal side effects from precision intensive proton beam therapy (not currently available in the UK for this disease) and photon radiation, may offer some hope to those weighing up treatment decisions.

Current evidence advocates total macroscopic surgical clearance followed by adjuvant high-dose radiotherapy for chordomas. However, the inherent proximity of vital neurovascular structures makes disease-free resection margins difficult to achieve and recurrence is common; ~66%, regardless of intervention used, and 100% within 2 years if inadequate margins are left or a subtotal resection is performed, or if radiation therapy alone is used. Presurgical radiotherapy may also be required, as in this case, to debulk the malignancy. The typical surgical procedure applied to skull-based chordomas is resection via an endonasal approach, which can carry great morbidity, particularly if seeding occurs in this region.

Surgical approaches offered in the UK were deemed unlikely to achieve complete resection, while causing great morbidity, so the patient was referred to a German centre with more expertise in chordoma surgery, where an unusual far right lateral transcondylar approach achieved complete macroscopic resection, with minimal adverse effects and rapid patient recovery. However, cervical fusion was later required and seeding of the tumour occurred, highlighting the complications and need for advance surgical consideration of these potential outcomes.

In summary, this case included a number of atypical approaches to treatment that are likely to be of interest to those concerned with this condition, including: the transcondylar surgical approach; application of proton radiotherapy not available at the time in the UK; concurrent chemotherapy and proton beam radiation; the use of a gene-marker targeted therapy regime; and the initial success of a sarcoma chemotherapy regimen in debulking the malignancy and clearing pulmonary metastases entirely.

CASE PRESENTATION

A 3-year-old boy presented with progressive neck pain over several months, holding his head in increasing neck extension. Cervical spine MRI revealed a tumour (2.5×2.5 cm) at the skull base along the edge of the foramen magnum, spreading onto the clivus, suggestive of chordoma. Immediately following this MRI, the patient developed quadriparesis, only retaining functional use of his right upper limb; movement provoked severe pain, and he held his head constantly at maximum extension. Staging CT showed 16 metastases in the lung bases.

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Figure 1 Left: initial MRI, right: MRI after several months of chemotherapy. Note the improved head position and debulking of the tumour mass.

Transoral biopsy tissue diagnosis was inconclusive; chordoma and poorly differentiated rhabdomyosarcoma were suggested. Owing to sarcomatous features and pulmonary metastases, it was treated as a sarcoma. A chemotherapy regimen followed including ifosfamide, vincristine, actinomycin D and doxorubicin.

MRI at 4 months demonstrated marked reduction in size of the primary tumour (figure 1) and CT showed the lungs were clear after 4 months of treatment. By this time, the patient had regained full power in all limbs. Biopsy review at a specialist centre gave a diagnosis of dedifferentiated chordoma.

Proton beam radiation treatment (PBT) of 74 Gray was administered to the primary tumour, with concurrent chemotherapy (cyclophosphamide and vincristine) to 'mop up' residual pulmonary disease. On completion, 15 Gray photon radiotherapy was given to the child's lungs followed by maintenance chemotherapy using cyclophosphamide, vincristine and actinomycin D. This was completed 18 months after initial MRI, with serial scans showing radiological clearance of lung metastases and minimal, inactive, residual primary tumour mass on cervical MRI.

After 18 months of radiological disease stasis, MRI revealed relapse of the residual primary clival tumour with intraosseous and extraosseous involvement, replacing the caudal half of the clivus, with extension into the prepontine cistern and hypoglossal canal (with resultant palsy), and involved the occipital condyles of C1/C2. The lungs remained clear of metastatic disease.

The patient underwent total macroscopic resection via a far right lateral transcondylar approach (figure 2). Pathology reported dedifferentiated chordoma with a high proliferation rate (30%). One sample had unusually high-grade cytological atypia, mitotic count and tumour necrosis, but brachyury expression excluded dedifferentiation (figure 3).

Craniocervical junction X-rays demonstrated stability, with neither cervical fusion nor neck needing support post surgery. The patient developed increasing neck pain during follow-up physiotherapy and began holding his head in right lateral flexion. MRI 6 weeks post surgery showed no disease progression but a CT scan revealed instability of the craniocervical junction (figure 4), which was urgently corrected with occipitocervical stabilisation (figure 5), relieving the patient's pain.

Post-stabilisation MRI revealed a 2 cm tumour in the soft tissue under the initial surgical scar, which was then resected.

Pathology reported metastatic chordoma; tissue removed from the primary clival tumour bed during stabilisation showed continuing disease activity.

With tumour progression in two locations, further local PBT therapy was no longer an option. The resected chordoma was analysed for genetic markers amenable to targeted therapy.¹ Primary and seeded tumours were both positive for p-S6RP, p-mTOR, p-AKT and PTEN. The seeded tumour was additionally positive for PDGFRb.

Targeted chemotherapy options were identified including sirolimus (S6RP and mTOR pathways) and imatinib (PDGFRb pathway).

Figure 2 The surgical wound 10 days post operation after macroscopic resection via a far right lateral transcondylar approach. The patient had made a good recovery by this time.

Figure 3 H&E-stained sections of the clival-based chordoma, showing the characteristic vacuolated cells but with atypical features. Left: the cells show nuclear pleomorphism and cells with large hyperchromatic nuclei more than is seen in a conventional chordoma (*). Right: at higher power magnification, the atypical appearance of the cells is revealed, with prominent nucleoli (*) contorted multilobation of nuclei (**) and a tri-polar mitotic figure (arrow).

Chest CT reported a solitary 3 mm spiculated lesion in the left lung apex and, a month later, an ultrasound scan identified a new tumour in the soft tissue of the neck under the primary surgery scar, measuring 1.61 cm×1.14 cm. These were chosen as markers for targeted therapy effect. Initially, sirolimus was used for 8 weeks. Follow-up CT showed the lungs to be clear, but an MRI revealed continued growth of the primary skull-base tumour. Imatinib was started hoping combined therapy would be more effective.

Follow-up CT scan 1 month into this approach showed tripling in size of the seeded tumours, and suspected new tumours in the lungs. The combined targeted therapy was ceased and the child was started on conventional etoposide chemotherapy. This was discontinued after 9 weeks due to little effect. He had 20 Gray of photon radiation to the cutaneous seeded tumours, with little effect. MRI showed significant recurrence of the primary tumour extending to involve the skull base and adjacent soft tissues.

Palliative care began 12 months after primary surgical intervention. Neurological deficits secondary to cranial nerve invasion and compression by the primary tumour included

neurogenic dysphagia for solids and liquids, hoarseness with bovine cough and poor vocal volume, left-sided tongue and hemifacial muscle wasting and lagophthalmos.

Seeded cutaneous tumours spread across the child's neck, the combined fungating mass growing to substantial size (~35×20×14 cm) at its largest (figure 6). This made positioning and sleeping difficult, and he required assistance to hold his head upright for extended periods of time. He became increasingly cachectic until he was no longer able to mobilise independently, and refused nasogastric feeding.

The patient died 6 months after initiating palliative care, aged 7 years, likely via brainstem herniation based on clinical assessment.

DISCUSSION

Chordoma is a rare, slow-growing, chemoresistant and radioreistant locally aggressive malignancy that arises from notochord remnants. It can occur anywhere along the spine. Peak incidence is in the 5th/6th decades of life. Less than 5% of cases occur under 20 years of age, the incidence of which is 1 per 250

Figure 4 CT scan demonstrating cervical instability. The skull and cervical spine should be at right angles to one another. Note the absence of part of the right side of C1, removed as part of the macroscopic resection of the relapsed chordoma.

Figure 5 Plain film radiograph showing cervical fusion metalwork in situ. The patient felt pain relief immediately on waking, and was comfortably mobile within a few days.

million.^{2 3} Dedifferentiation occurs in <5% of cases.⁴ Diagnosis in patients under 5 years of age has worse prognosis with greater aggression and dissemination.^{2 5-7} Metastases occur in about 10% of cases.⁸ This case therefore represents a rare and particularly aggressive variant of an already rare and aggressive disease.⁹

Current evidence advocates total macroscopic surgical clearance followed by high-dose radiotherapy. The inherent proximity of neurovascular structures such as the spinal cord make disease-free resection margins difficult to achieve; recurrence is

Figure 6 Cutaneous seeding of the poorly differentiated chordoma, originating from under the surgical wound shown in [figure 2](#).

100% within 2 years with either inadequate margins or subtotal resection, or radiation therapy alone.^{4 10} Presurgical radiotherapy may be used to de-bulk disease.^{11 12} PBT often has a larger role in clival disease control, as high-dose radiation can be delivered precisely to the target area—with reduced damage to surrounding neurovascular tissue—compared to traditional photon radiation.^{7 9} Cutaneous seeding is a recognised complication of surgery, especially with poorly differentiated tumours.¹³

Unlike conventional chordoma, the dedifferentiated subtype appears to be more responsive to chemotherapy.^{5 14 15} In this case, chemotherapy achieved complete resolution of pulmonary metastases and primary tumour debulking prior to PBT. After PBT, the patient recovered quickly and fully, having excellent quality of life for 18 months. With relapse, the greatest morbidity came from the seeded tumour. Awareness of this important surgical complication is emphasised.

Comparable cases are limited. This child's survival from diagnosis with metastasis was 54 months. Two cases of dedifferentiated chordoma in young patients from another study had worse survival; a 25-year-old girl with sphenoccipital disease died within 6 months, and a 16-year-old boy with mobile spine

Patient's parent's perspective

- ▶ Both parents: We feel more credence should be given to parents when a child presents with unusual symptoms and there is no history of the child being a hypochondriac. Getting the first scan that revealed that the cancer took months, with our child's painful stiff neck getting worse, and being sent home from consultation after consultation with reassurance all was fine. This was our sixth child, and there was no history of being overly anxious parents with the others. We were also told our child was very 'petted' before the scan result returned. Doctors should choose their words carefully.
- ▶ Consultants should not be too dismissive of parents' own research on rare diseases; a consultant typically has a large number of patients while parents have (hopefully) only one sick child, thus more time and invested interest.
- ▶ We were able to get world experts on board willing to consult with our local team, who had experience researching and treating this extremely rare cancer. However, a team approach was needed and we don't feel we got the benefit of this, having to indirectly liaison as middle-men between the experts and our local team.
- ▶ Father: I feel the seeded subcutaneous tumour in our son's neck should have been removed each time it reappeared, for his comfort, even in a palliative care scenario. It became so large, weighing more than his head, and adding hugely to his discomfort over several months before he died.
- ▶ Mother: My husband and I disagreed on much of my son's treatment and, looking back on this, I would not have done the primary surgery. I feel the surgeon did an amazing job, but, we were only 'buying time'. The last 6 months of his life were horrific due to seeding from the removal of the tumour.
- ▶ Father: The novel approach of chemo followed by proton beam treatment (PBT) achieved a good quality of life for the interim period and was definitely worth it; the surgery would also have been if we had been able to follow-up with PBT or better administered targeted therapy.

Learning points

- ▶ Increasing intractable neck pain is a red flag presentation, particularly in patients under the age of 20 years. In the absence of trauma, a more common cause such as torticollis would not be expected to last longer than around 2 weeks.
- ▶ The patient's mother presented several times to services, failing to be reassured, seeing a progressive deterioration in her child. The authors emphasise appreciation of a parent's familiarity with 'normal' for their child, as an important consideration in any paediatric presentation.
- ▶ A transient quadraparesis occurred after initial MRI under general anaesthetic, and cervical destabilisation followed physiotherapy and another MRI, after primary surgery. These reinforce the need for great care when altering the adopted head position of an unconscious patient with suspected neck pathology, and post-cervical spine surgery.
- ▶ The patient had an excellent response to chemotherapy and proton beam radiation, achieving complete metastatic clearance, tumour debulking and disease stasis, initially giving excellent quality of life. This case adds to the evidence supporting chemotherapy and proton beam treatment in poorly differentiated and metastatic paediatric clival chordoma.
- ▶ Cutaneous seeding caused great morbidity post surgery until the patient's death. An emphasis on this potential complication for dedifferentiated chordoma is stressed.

disease and pleural metastasis died within 40 months.¹⁶ Our patient survived 9× and 1.35× longer than these cases, respectively. In another study including two cases with dedifferentiated clival disease: one child survived 39 months having had partial resection, intensity modulated radiotherapy, etoposide, ifosfamide, liposomal, doxorubicin, gleevec and celebrex. The other was alive at 6 years post diagnosis, with stable residual tumour, following partial resection, PBT and a chemotherapy regime of ifosfamide, etoposide, celebrex and gleevec.⁵ Note the similarities in management of the cases with better outcomes, and that of our patient. These may represent an effective combination and order of treatment for prolonging life, and a direction to pursue further study.

Numerous aspects of this case were atypical, but may indicate areas for improving management in this aggressive form of the disease. These include an initially excellent response to the chemotherapy regime with complete metastatic clearance and tumour de-bulking, concomitant chemotherapy and PBT, complete macroscopic surgical clearance via a far right lateral approach and the use of targeted therapy.

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Competing interests Both authors are related to the patient. To help mitigate any potential conflict of interest, we have had the paper additionally reviewed by Dr Anthony McCarthy (Consultant Oncologist in charge of the case) and two experts in this disease who consulted on the case: Professor Norbert Liebsch and Professor Adrienne Flanagan.

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