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Leukaemic infiltration of the mandible in a young girl

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Background. This report presents a case of leukaemic infiltration of the mandible in a 10-year-old female of Sudanese extraction.

Case report. The patient was in remission from acute lymphoblastic leukaemia when she presented with pain localized to the alveolar ridge overlying the unerupted lower right second permanent molar. Two days later, she developed right inferior alveolar nerve paraesthesia. Radiographic imaging demonstrated cortical line absence around the developing lower right second and third permanent molars, and distal displacement of the lower right third molar. In addition, the cortical outline of the right inferior dental canal lacked clarity. Biopsy confirmed leukaemia recurrence demonstrating the Philadelphia chromosome. Tailored chemotherapy was commenced, and a bone marrow transplant was carried out 12 weeks later. At 6-month dental review, the patient remained exceptionally well with no bone pain and normal sensation in the right lower lip.

Conclusion. The importance of regular and long-term dental examination of patients with leukaemia is discussed.

Introduction

Leukaemia constitutes one-third of all childhood cancers and three-quarters of that group of paediatric patients suffer from acute lymphoblastic leukaemia (ALL), which may be of B or T cell origin. Childhood leukaemia has a UK incidence of 450 new cases per year with a peak incidence between 2 and 5 years of age, and a higher prevalence has been reported in males[1,2].

The aetiology of leukaemia remains speculative, although a number of factors have been implicated including: exposure to ionizing radiation or electromagnetic fields, treatment with cytotoxic drugs and viral infections[3]. Treatment for ALL involves complex, tailored chemotherapeutic regimes comprising an induction stage, consolidation and central nervous system (CNS) treatment, and at least 2-yearly maintenance phases. Patients will almost certainly be treated as part of a clinical trial, such as the current Medical Research Council UK ALL trial[2].

In the 1960s, the long-term survival for childhood ALL was expected to be around 4%, but in recent years, the cure rate has risen dramatically to 75–80%[2]. However, several subgroups with a poorer outcome can still be identified[2,4–6]. Moricke and co-authors[4] found that event-free survival (EFS) was significantly associated with age. The most unfavourable outcome was found in infancy cases with a 45% 8-year survival rate. The best EFS rates were achieved at preschool age (1–5-year-olds, EFS = 82%). After 5 years of age, the EFS again decreased (6–9-year-olds, EFS = 75%; 10–14-year-olds, EFS = 63%). A number of genetic alterations are present in both B and T cell ALL, and these are important in disease prognosis. In childhood precursor B cell ALL, between 3% and 4% demonstrate the Philadelphia chromosome (Ph-chromosome, a 9;22 translocation), 2–3% a 4;11 translocation and 6% a 1;9 translocation. These cases are all more resistant to conventional therapy and indicative of poor long-term prognosis[5,6].

Almost one-quarter of children achieving remission from ALL will relapse, and relapsed disease is often more resistant to treatment[2]. Relapse can affect the bone marrow or extramedullary sites. If the bone marrow is affected, the prognosis is poorer. Extramedullary relapse often involves leukaemic cell proliferation in the cerebrospinal fluid (CSF) and in the testis in males. Just 3% patients have leukaemic cells in the CSF at

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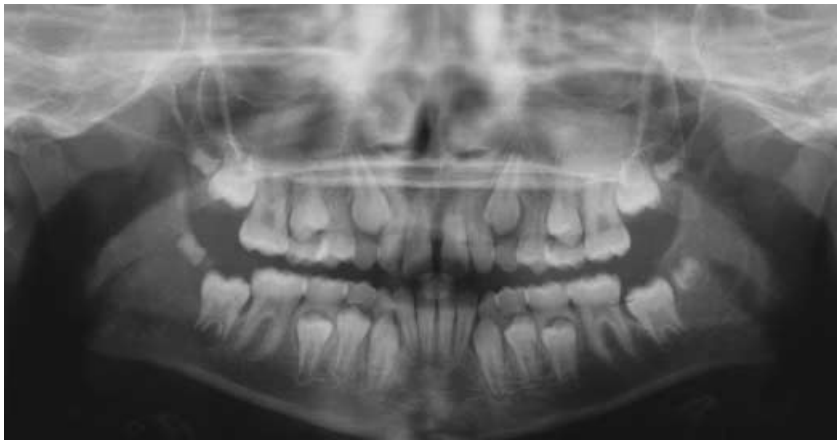

Fig. 1. Dental panoramic tomograph showing the presence of distal and occlusal displacement of the lower right third permanent molar and poor demarcation of the right inferior dental canal.

diagnosis, but without CNS-directed preventive therapy involving intrathecal methotrexate, 50–75% of children will develop CNS disease[2].

Oral complications occur frequently in leukaemia and may, indeed, be the presenting feature of the disease[8,9]. Oral manifestations usually arise from an underlying thrombocytopenia, neutropenia or impaired granulocyte function, or may result from direct leukaemic infiltration. Previous reports have described a number of leukaemic-induced oral changes including: pain; gingival swelling; bleeding; ulceration; bony changes; and infection[8,10]. However, oral manifestations specifically associated with a recurrence of ALL have been infrequently documented in the literature[9,11].

This case report describes leukaemic infiltration of the mandible in a young girl as the first indication of ALL recurrence.

Case report

In March 2005, a 10-year-old female of Sudanese extraction was urgently referred to the Paediatric Dentistry Clinic of the Charles Clifford Dental Hospital, Sheffield, UK, by the oncology team at the nearby children's hospital for an opinion regarding her reported oral pain. The patient was already known to the Paediatric Dentistry Clinic and had been a regular attender over the previous 3 years with an uneventful dental history. She had last been seen in September 2004 with no oral complaints other than some discomfort from the eruption of the upper left first premolar. Bitewing radiographs were taken at that appointment, and these showed no abnormalities.

The presenting complaint was of pain, localized to the alveolar ridge overlying the unerupted lower right second permanent molar, that had been present for 4 weeks. The pain was described as a severe and continuous ache that had disturbed the girl's sleep and required analgesics. The patient had been concurrently treated for an infection of the right ear, but the oral symptoms had reportedly preceded the ear complaint.

The patient had a significant medical history, having been diagnosed with precursor B cell ALL in January 2002, following a 6-month history of bone and joint pain. The patient subsequently underwent a 2-year course of chemotherapy, achieved remission and remained under monthly recall with the paediatric haemotological oncology team. The patient had remained well and symptom-free until the onset of this current orofacial pain.

Clinically, there were no extraoral findings of note. Intraoral examination revealed a mixed dentition, which, together with the soft tissues, appeared healthy. There was reported tenderness on palpation of the right retromolar region, but there were no visible signs of any pathology.

A dental panoramic tomograph (DPT) and periapical film of the unerupted lower right second permanent molar were taken (Figs 1 & 2). A consultant dental radiological report highlighted the absence of the cortical line around the developing lower right second and third permanent molars. The lower right third molar was displaced distally and occlusally. In addition, the cortical outline of the right inferior dental canal was unclear when compared to the contralateral side, which was well

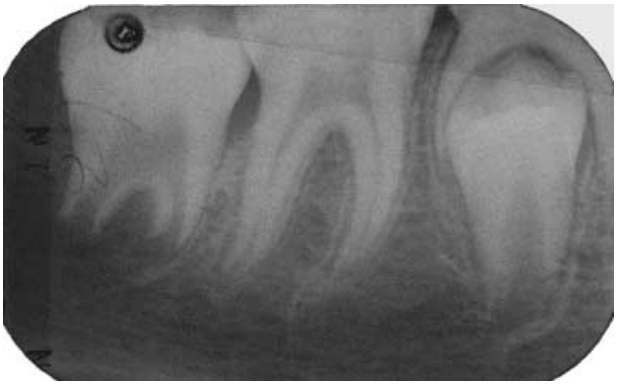

Fig. 2. Periapical radiograph showing absence of the cortical line around the developing lower right first and second permanent molars.

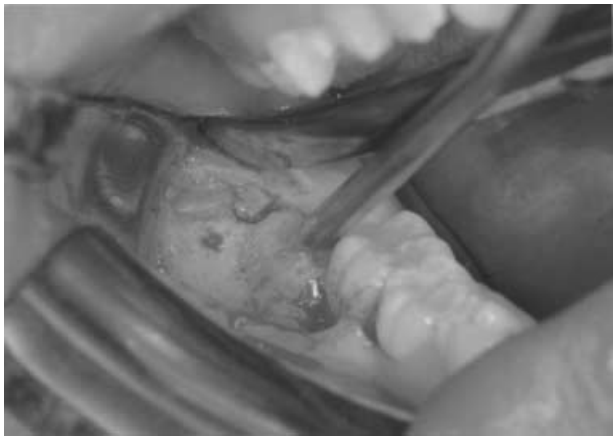

Fig. 3. Clinical photograph showing the buccal mucoperiosteal flap raised distal to the lower right first permanent molar, revealing the intact cortical plate.

demarcated. Additional observations were made regarding the diminutive third permanent molars and obliteration of pulp chambers in the primary molars. These latter features were attributed to the effects of previous chemotherapy given the patient's medical history. However, the unusual radiological appearance of the right mandible was suggestive of a leukaemic infiltrate and further medical investigation was urgently advised. Two days later, the patient presented to the oncology team with loss of sensation to the skin and lip of her right chin area. She also complained of left thigh and shoulder pain.

Surgical management

A biopsy of the right mandible was carried out that same week under general anaesthetic along with a lumbar puncture and bone marrow aspirate. A buccal mucoperiosteal flap was raised distal to the lower right first permanent molar (Fig. 3). The lower right third molar was encased by a thick layer of soft tissue which was easily curetted from the surrounding bone. Both the third molar and a sample of the soft tissue were sent for histopathological examination.

Histopathology

Biopsy from the right mandible showed cellular fibrous tissue with proliferating odontogenic epithelium and spicules of calcification. A small leukaemic focus was present at one

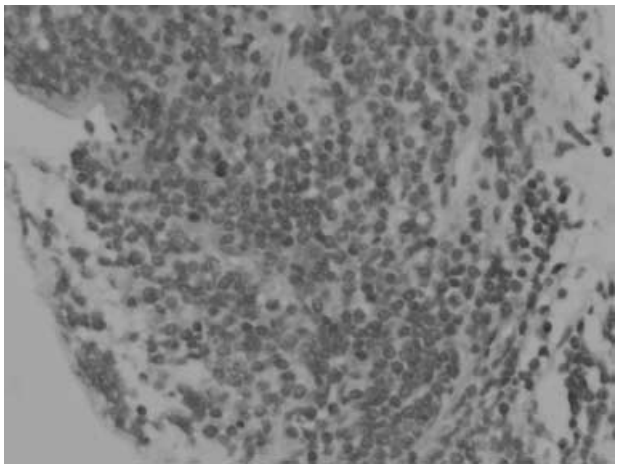

Fig. 4. Clinical micrograph showing leukaemic infiltrate in a specimen from the right mandible (magnification × 40).

margin, comprising small cells with round-to-ovoid nuclei and condensed chromatin, and very little cytoplasm. Occasional cells were larger, with vesicular nulclei and prominent nucleoli (Fig. 4). Occasional mitoses were seen. A recurrence of precursor B-lymphoblastic leukaemia was confirmed with positive staining for CD20 (focal), CD10, TdT (terminal deoxynucleotidyl transferase) and CD24.

Other causes of a small round cell tumour with a similar morphology in a child include rhabdomyoblastoma, Ewings sarcoma, leukaemia with different chromosomal expressions, melanoma and carcinoma. These were excluded by stains for cytokeratin (AE1/AE3), CD3, desmin,

myogenin, NSE, CD4, S100 and CD99. The extracted right mandibular third molar contained no evidence of a neoplastic infiltrate. Bone marrow aspirate also confirmed relapse, but the cerebrospinal fluid was clear of abnormal cells.

Medical management

The definitive diagnosis was of a relapse of precursor B-ALL which showed the prognostically unfavourable Ph-chromosome t(9;22). Imatinib and dexamethasone tailored chemotherapy was commenced. Initial and consolidation-stage therapy with imatinib achieved an excellent molecular response with a 4-log reduction in tumour burden. Within 24 days, there was an almost complete clearance of blasts from the patient's marrow and restoration of normal haemopoiesis, as found in 70% of Ph+ childhood ALL cases treated with imatinib by Champagne and co-authors[12].

A matched sibling allograft bone marrow transplant (BMT) was carried out 12 weeks after the initial confirmation of relapse, without the need for further conventional chemotherapy. Post-transplant complications were limited to cyclosporin-related headaches, and grade II skin and graft versus host disease.

Dental review

The patient was reviewed a few days after surgery and showed good intraoral healing. At her 6-month dental recall, she remained exceptionally well, with no bone pain, and sensation in the right lower lip had returned to normal. The patient recommenced full-time school in January 2006, and remains under close dental and medical review.

Discussion

Osseous changes, in association with the initial onset of leukaemia, have been well documented[13,14]. As some haematopoietic activity remains in the mandible of a child, there is potential for leukaemic infiltration of this bone. Curtis[13] reviewed 214 DPTs of children with acute leukaemia and found several disease-related changes. He reported a high degree of correlation between radiographic destruction or altered radiodensity of alveolar bone, and clinical evidence of leukaemia. Other radiographic changes included destruction of bony crypts around developing teeth, and thinning or disappearance of the lamina dura of erupted teeth. Differential diagnoses of these radiographic changes may include osteomyelitis and osteoradionecrosis, particularly when irradiation therapy has been used[15].

There are very few documented reports of leukaemic infiltration following disease relapse in children with which to compare the presented case. However, Williams and colleagues[15] described two cases of mandibular involvement in children. The first case was of a 6-year-old girl who had completed chemotherapy and radiotherapy for ALL. She had been in disease remission for a year when she was seen with presumed dental abscesses despite a lack of clinical caries. The symptoms progressed to severe left-sided facial pain and a swelling adjacent to the upper left second deciduous molar. Her DPT revealed a radiolucency distal to the unerupted upper left second premolar that was displaced within its crypt. Histological examination of the specimen was consistent with a non-Hodgkin lymphoma. The second patient was a girl aged 12 years who had been in remission from ALL for 2 years. She presented with paraesthesia of the right inferior dental nerve and a swelling adjacent to the lower right second molar. The DPT revealed 'pencil sharpening' and resorption of the roots adjacent to a radiolucent region in the lower right molar region. Histology was consistent with a non-Hodgkin lymphoma.

Children are less likely to complain about altered orofacial sensation than adults, and thus, there may be a more prolonged period of reduced sensation prior to profound anaesthesia, and hence, delayed detection. This provides an argument for routine screening for early signs of relapse in children, which is particularly important for patients with disease of a poorer prognosis. Collard and Hunter[16] examined the provision of oral and dental care for children receiving treatment for ALL in the United Kingdom Children's Cancer Study Group (UKCCSG) centres. They found that almost one-quarter of these centres did not have an oral care protocol. In the main,

patients were referred to the local dental hospital and it was suggested that the development of dental services at tertiary referral centres should be vigorously pursued. Collard and Hunter[17] also looked at dental care in patients with ALL from the patients' and parents' point of view. They found that around two-thirds of parents expressed a wish for dental care to be carried out within the paediatric oncology unit. Offering dental care on the same day as oncology clinic appointments is time-efficient and avoids unnecessary stress in the difficult circumstances posed following diagnosis and during treatment. The above authors suggested that healthcare professionals should follow protocols with an emphasis on prevention.

The UKCCSG[18] suggests the use of a bone mineral density DEXA scan in ALL survivors, and the present patient received this. Williams and co-authors[15] recommended DPT radiographs as appropriate diagnostic tests for patients with leukaemia and oral symptoms including paraesthesia, pain and swelling. However, the routine use of DPTs as screening tools for detection of disease relapse is debatable, and there are no clinical guidelines to support such an approach. Furthermore, radiation protection guidelines discourage 'routine' radiographs because every radiation exposure carries risks (a DPT has a 1:1 000 000 chance of causing a malignancy) and must be weighed against the potential benefit to the patient.

What this paper adds

- The presenting complaint and radiographic changes associated with leukaemic infiltration of the mandible in a young patient with disease recurrence are described.
- A brief update is given on the implications of Ph-chromosome-positive ALL and the medical management of children with this condition.

Why this paper is important to paediatric dentists

- This paper highlights the requirement for regular dental reviews of patients with ALL, given the oral complications associated with the disease and the potential for oral symptoms to be the first indication of a relapse.
- The authors demonstrate the benefit of rapid communication and action between dental and medical professionals in reaching a diagnosis and instigating appropriate care to ensure the best possible outcome for young oncology patients.

Conclusion

The authors hope that this report serves as a reminder to those caring for survivors of childhood leukaemia, particularly dentists, to be vigilant regarding complaints of jaw pain or numbness. Although jaw pain may be of dental origin or the result of a side-effect of chemotherapeutic agents, it may also be a sign of disease recurrence.

A DPT would usually be the most appropriate way to identify leukaemic changes. A consultant in dental and maxillofacial radiology should be asked to provide a radiographic report since the changes seen in leukaemic infiltration can be subtle. The patient's oncologist should be immediately contacted if there is any suspicion of disease recurrence. It is also suggested that ALL patients should be under regular dental review, ideally in a specialist centre, as part of their multidisciplinary care[16,17].

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