Anaplastic large cell anaplastic lymphoma kinase + non-Hodgkin lymphoma in a 10-year-old male discovered during dental visit: a case report

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Abstract
Non-Hodgkin lymphoma is rare in children, even though it is the third most frequent type of tumour. Management of a child with non-Hodgkin lymphoma is complex and coordinate presence of haematologists, surgeons, radiotherapists, neurologists, psychologists and other expert personnel is required.

Our patient presented with a bulky mass of approximately 5 cm in diameter, which grew from his upper-left maxillary bone, thereby causing gum bulge. Thus, the left side of his face from lip to eye appeared swollen. A whole body computed tomography–positron emission tomography examination revealed that the mass was growing in the mouth and maxillary bone and that many bulky nodes were present both in the right and left neck. Histological haematoxylin and eosin assessment revealed an anaplastic large cell proliferation underlyng the epithelial tissue without epithelial infiltration.

The patient underwent a first cycle of chemotherapy according to the 'International Protocol of anaplastic large cell lymphoma'. The Maxillofacial Surgery Unit and the Dentistry Unit of the same hospital took care of his dental situation to avoid the spread of infective foci to the entire body.

After 1 year and 3 months from the first cycle of chemotherapy, a bulky splenic mass was discovered. Laparoscopic biopsy revealed a relapse of the anaplastic lymphoma kinase-positive anaplastic large cell lymphoma in a splenic node. The patient is now alive in good conditions, and continuously followed-up by the Pediatric and Hemato-oncology Operative Unit of University Hospital of Parma.

Rapidity of action and a correct multidisciplinary (oncology-maxillofacial surgery-dentistry) approach is the key to cure illness, promptly diagnose relapse and avoid the spread of infective foci from the patient's teeth during chemotherapy cycles.

Introduction
Non-Hodgkin lymphoma (NHL) is rare in children, even though it is the third most frequent type of tumour. Management of a child with NHL is complex and coordinate presence of haematologists, surgeons, radiotherapists, neurologists, psychologists and others expert personnel is required. Moreover, social workers and nurses are very important in granting the best quality of life to the patient and to fasten rehabilitation. Thus, children with NHL should be treated in reference centres with proper experience.

The dissemination of NHL has been put in correlation with patients' prognosis. For this reason, early diagnosis can lead to a dramatic increase in the patient's probability of disease-free survival. When a patient realises that there is something unusual orally, he generally visits a dentist. The dentist would carefully inspect oral soft tissues and routine radiographic examination may demonstrate an ongoing disease; thus, dentists play a key role in the preliminary detection of NHL.

Histological classification of paediatric NHL
Histological classification of paediatric NHL is simpler than conventional adult NHL classification. Indeed, almost every case of paediatric NHL belongs to high malignancy grade lymphomas and can be classified into three histological patterns: follicular lymphoma, Burkitt's lymphoma and anaplastic large cell lymphoma (ALCL).

In each of these histological patterns, different subtypes can be recognised. Diagnosis of first two patterns can be difficult if the marrow is affected; in case neoplastic cells reach ≥25% (30% according to some authors), the disease is classified as lymphoblastic acute leukaemia. This distinction makes no difference in terms of therapy.

Staging and presentation modes
Paediatric NHL staging procedure is similar to adult NHL staging procedure; the sole difference is represented by the role of surgery. Indeed, paediatric NHL presents with bulky abdominal or mediastinal masses; therefore, in many cases, exploratory laparoscopy is used to harvest biopsies, especially when superficial nodes cannot be harvested for biopsy.

Pathological masses are usually harvested during abdominal surgery as according to many studies, prognosis...
Case report

Paediatric NHL therapy

Multidisciplinary approach is necessary for paediatric NHL. Chemotherapy is the gold standard approach, as we consider the disease to disseminate from the beginning even in apparently localised cases. Many different protocols have been proposed, which are sometimes very complex and recommend up to 4–10 different drugs.

Radiotherapy has a marginal role in paediatric NHL. It is sometimes used before chemotherapy when rapid reduction of mediastinal tumour masses is required. In recent studies, radiotherapy was omitted from treatment programs to attempt to reduce the incidence of long-term side effects in patients treated with a combined therapy involving chemotherapy and radiotherapy.

Since few years, prognosis of children with NHL has remarkably improved. Worldwide, 60%–70% of children with NHL have a 5 year disease-free prognosis; the percentage has increased to 90% in some subtypes. Recurrences (uncommon, 30%) are treated with a different protocol and often remain sensitive to chemotherapy. Allogeneic or autologous bone marrow transplant may be considered, but it is still considered to be an experimental procedure, lacking long-term efficacy data.

Case presentation

A 10-year-old boy visited the University of Foggia Dental Clinic as recommended by his dentist. He visited his dentist for check-up of a rapidly growing intra-oral mass in the upper-left maxilla. The patient came to our observation with a bulky mass, approximately 5 cm in diameter, which grew from his upper-left maxillary bone, thereby causing gum bulge. Thus, the left side of his face from lip to eye appeared swollen. A whole body computed tomography–positron emission tomography (CT-PET) examination was required. This revealed that the mass was growing in the mouth and maxillary bone and that there were many bulky nodes both in the right and left neck.

An incisional biopsy of the gum and underlying tissue (approximately 1.5 cm in diameter) was performed. Beneath the gum, instead of bone, surgeons found an amorphous lymphoid-like soft tissue. The sample then underwent histological and immunohistochemical examinations. Histological haematoxylin and eosin (H&E) assessment revealed an anaplastic large cell proliferation underlying the epithelial tissue without epithelial infiltration. Thus, immunophenotypisation was performed for checking positivity for a series of markers (Table 1). Immunohistochemical staining results are shown in Figure 1.

Tumour cells were positive for epithelial membrane antigen (EMA), and they stained positively for CD30. They were also positive for Ki-67, showing very high proliferation index (70%). Finally, positivity for anaplastic lymphoma kinase (ALK) directed us towards a diagnosis of ALK-positive ALCL (ALK+ ALCL). This is a T-cell lymphoma, which is very rare in adults (about 3% of NHLs) but quite frequent in children (10%–20% of all lymphomas). It frequently involves extranodal sites such as skin, soft tissues, lung, liver and—as in this case—bone.

The patient was immediately sent to the Department of Mother–Child, Pediatric and Hematology-Oncology Operative Unit, University Hospital of Parma, where he could be treated with the necessary multidisciplinary approach. The patient underwent a first cycle of chemotherapy according to the ‘International Protocol of ALCL’. The Maxillofacial Surgery Unit and the Dentistry Unit of the same hospital took care of his dental situation to avoid the spread of infective foci to underlying the epithelial tissue without epithelial infiltration. Thus, immunophenotypisation was performed for checking positivity for a series of markers (Table 1). Immunohistochemical staining results are shown in Figure 1.

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<table>
<thead>
<tr>
<th>Antibody</th>
<th>Immunohistochemical staining</th>
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<tr>
<td>Myeloperoxidase</td>
<td>Negative</td>
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<tr>
<td>Myoglobin</td>
<td>Negative</td>
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<tr>
<td>CD30</td>
<td>Positive</td>
</tr>
<tr>
<td>CD10</td>
<td>Negative in neoplastic cells, positive in surrounding cells</td>
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<tr>
<td>CD3</td>
<td>Positive</td>
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<tr>
<td>CD2</td>
<td>Negative in neoplastic cells, positive in surrounding cells</td>
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<tr>
<td>CD20</td>
<td>Negative</td>
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<tr>
<td>CD79a</td>
<td>Negative in neoplastic cells, positive in surrounding cells</td>
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<tr>
<td>TdT</td>
<td>Negative</td>
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<tr>
<td>ALK-1</td>
<td>Positive</td>
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<td>EMA</td>
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Table 1. Immunohistochemical findings of ALK+ ALCL case.

is best when each visible mass is harvested.

Many different paediatric NHL staging systems exist. The most commonly used staging system is the one used at the Saint Jude Children’s Research Hospital.

Two emergency situations occur more often in paediatric NHL cases than in adult NHL cases:

- Obstruction of superior vena cava syndrome, more frequently in lymphoblastic lymphoma, caused by bulky tumour masses compressing the airways and other mediastinal structures
- Acute tumour lysis syndrome, more frequently in Burkitt’s lymphoma, caused by the release of ‘toxic’ molecules from neoplastic cells.

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All authors contributed to the conception, design, and preparation of the manuscript, as well as read and approved the final manuscript.

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the entire body. Two teeth were extracted and professional hygiene was performed every month; antibiotics were prescribed as and when required. RM, CT, PET and eco exams were performed to check the status of primary lesions and detect possible relapses and neck node status, which were found to be mildly positive. After five months, the primary lesion was undetectable, but the right neck node remained mildly positive. A ‘wait and see’ policy was adopted.

After 1 year and 3 months from the first cycle of chemotherapy, a bulky splenic mass was discovered. Laparoscopic biopsy revealed a relapse of ALK+ ALCL in a splenic node. The patient thus was cured according to the ‘Italian Association of Pediatric Hematology-Oncology ALCL Relapse’ protocol under continuous dental care to prevent the spread of infective foci to the entire body. The patient is now alive in good conditions, is continuously followed-up by the Pediatric and Hemato-oncology Operative Unit of University Hospital of Parma. His dental condition is under surveillance by the Dentistry and Maxillofacial Surgery Units.

**Discussion**

The historical background of ALCL began in 1982 when the monoclonal antibody Ki-1 was raised against a Hodgkin’s disease (HD) cell line. Ki-1 was subsequently shown to stain the malignant cells of HD in tissue sections as well as a smaller lymphoid cell was found in the parafollicular regions of normal lymph nodes. The Ki-1 antigen, subsequently assigned to the CD30 cluster, was identified as an activation antigen, which could be expressed on T-cells, B-cells and even activated histiocytes.

In 1985, Stein et al. found that the Ki-1 (CD30) antigen was highly expressed by a group of 45 large cell lymphomas that shared a number of histological characteristics. These tumours exhibited a morphology which was suggestive of ‘malignant histiocytes’ and also exhibited prominent sinusoidal invasion. It was proposed that the anaplastic CD30-positive tumours represent a distinct clinicopathological entity; this was subsequently included in the revised Kiel classification in 1988 as ‘large cell anaplastic lymphoma’. The term ‘anaplastic large cell lymphoma’ ultimately became the preferred designation. The pathogenesis of ALCL was unravelled in 1994 when Morris and colleagues cloned the genes involved in translocation, identifying a newly described tyrosine kinase namely ‘anaplastic large cell lymphoma kinase’ (ALK).

ALCL has been defined as a distinct clinicopathological entity based on its histological, clinical, immunophenotypical, and molecular features. Molecular analysis has been an important tool in clarifying the borders of this and other entities, as most diseases have a distinct molecular fingerprint that relates to underlying pathogenesis. Moreover, in this paradigm, molecular studies may be used to refine the ultimate morphologic definition, leading to improved diagnostic criteria. The accurate diagnosis of ALCL has important clinical implications because it is a highly treatable form of lymphoma and has a much better prognosis than other types of T-cell lymphoma, even in case of relapses as observed in this case, unlike ALK-negative ALCL.

**Conclusion**

- Rapidity of action and a correct multidisciplinary (oncology-maxillofacial surgery-dentistry) approach is the key to cure illness, promptly diagnose relapse and avoid the spread of infective foci from the patient’s teeth during chemotherapy cycles.
- General practitioners/paediatric dentists and orthodontists have a key role in diagnosing soft tissues/bone neoplasms of the jaw. An accurate inspection of oral soft tissues and radiographic examination can easily lead to the discovery of abnormal conditions during routine visits to private practices.

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• For these reasons, dentists must not underestimate their importance in early diagnosis of oral and maxillofacial neoplasms.

**Abbreviations list**
ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; EMA, epithelial membrane antigen; HD, Hodgkin’s disease; NHL, non-Hodgkin lymphoma.

**Consent**
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

**References**