

# Development of non-Hodgkin's lymphoma in a child with hyper IgE syndrome

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## حدوث ورم لمفاوي بطفل مصاب بمتلازمة الزيادة المفرطة في الجلوبيولين المناعي س

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الملخص: تسجل هذه الورقة لأول مرة حدوث ورم لمفاوي من نوع "غير داء هودجكن" بطفل في السابعة من عمره يعاني من متلازمة الزيادة المفرطة في الأجسام المناعية المضادة. وهذه المتلازمة النادرة هي نوع من نقص المناعة الأولي الوراثي والتي تتميز بزيادة مفرطة الجلوبيولين المناعي (س) مع وجود حساسية جلدية مزمنة وغير عادية بالإضافة إلى التهابات جرثومية خطيرة ومتكررة إلى جانب وجود نسبة طبيعية من الأجسام المناعية المضادة الأخرى وزيادة مفرطة في كريات الدم البيضاء الليفية الأيوسين.

**ABSTRACT:** This paper reports development of non-Hodgkin's lymphoma in a 7½-year-old patient with hyper IgE syndrome. This rare primary immunodeficiency syndrome is characterized by markedly elevated serum IgE levels, chronic atypical dermatitis and serious recurrent infections. Laboratory features include exceptionally high levels of IgE, near normal levels of IgG, IgA, IgM, with pronounced eosinophilia.

**KEY WORDS:** Hyper IgE syndrome, tumours, lymphoid

**H**yper IgE syndrome is a rare complex disorder characterised by markedly elevated serum IgE levels, chronic dermatitis and serious recurrent infections.<sup>1</sup> In 1966, it was initially described as 'Job's Syndrome'.<sup>2</sup> Since then more cases have been reported.<sup>3,4</sup>

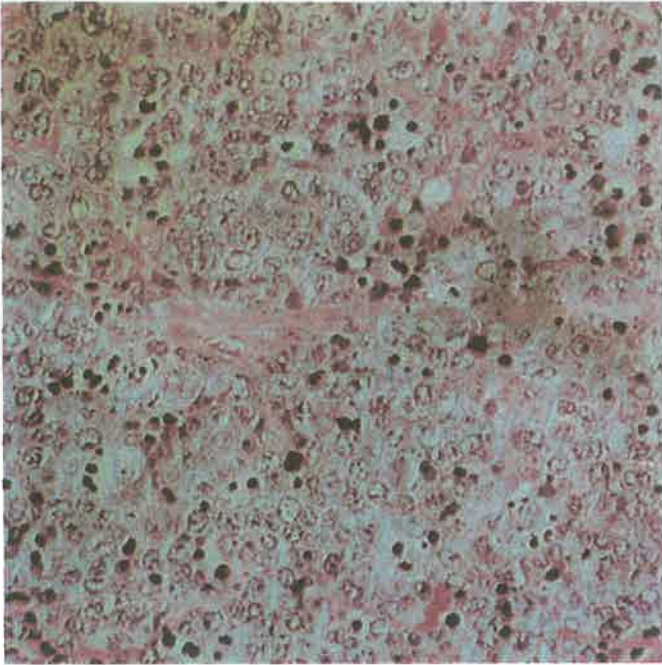
Even more rare are cases where hyper IgE syndrome patients develop lymphoid malignancy. Only five such cases are on record. Kowalchuk reported a superimposed lymphoma in a patient with Job's syndrome.<sup>5</sup> Hodgkin's disease was observed in two patients with hyper IgE syndrome.<sup>6</sup> Burkitt's Lymphoma was observed along with hyper IgE syndrome, in a 7 year-old boy.<sup>7</sup> Bale and associates reported the case of a 10 year old boy who developed a fatal histiocytic lymphoma of the brain.<sup>7,8</sup>

### THE CASE

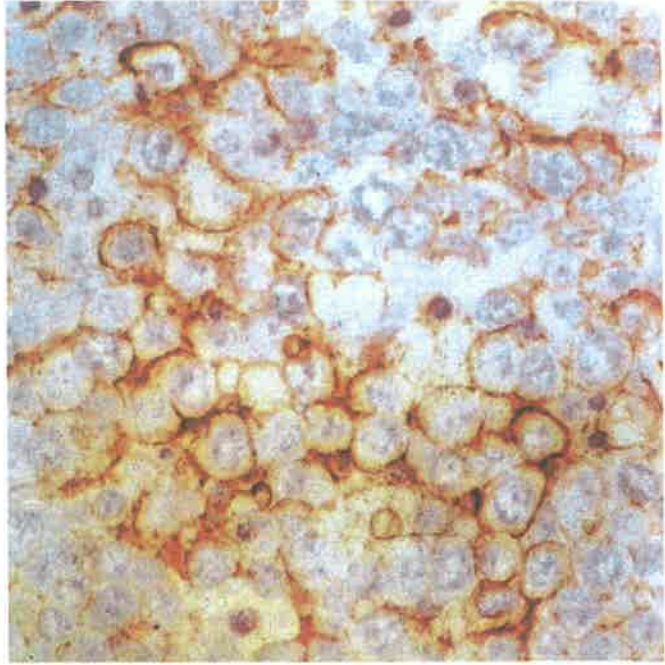
The patient was referred to us first at the age of 3 with history of recurrent chest infections and pruritic urticaria since infancy. He was severely underweight and had oral thrush, urticaria, fungal paronychia, suppurative otitis media and bronchopneumonia. Since then he had been repeatedly admitted with recurrent staphylococcal, streptococcal and salmonella septicaemia, bronchopneumonia, and multiple cutaneous abs-

cesses. Investigations repeatedly showed pronounced eosinophilia of  $> 20 \times 10^9/l$ . IgE level  $> 26,000$  KIU/l; Normal IgG subclasses; IgA and IgM levels frequently low; positive *Staphylococcus aureus*-specific IgE antibodies; nitroblue tetrazolium and phagocytic function tests normal. Flowcytometry showed reduced CD4/CD8 ratio with very low CD4 count. CD8 cells consisted entirely of cytotoxic/killer cells (CD8+/S6F1+) with zero level of suppressor subsets (CD8+/S6F1+). HIV status was repeatedly negative. At the age of 7½, the child presented with a superficial, firm, non-tender swelling, 2 cm in diameter, in the left preauricular and subauricular areas. There was no significant cervical axillary or inguinal lymphadenopathy. His liver was 8 cm and spleen 5 cm below the costal margins at the mid-clavicular lines. Investigations showed haemoglobin to be 9.5 g/dl, total white blood cells count  $21.8 \times 10^9/l$ , neutrophils  $7.5 \times 10^9/l$ , lymphocytes  $2.9 \times 10^9/l$ , eosinophils  $11.4 \times 10^9/l$  and platelets  $315 \times 10^9/l$ . Computer tomography of the chest, abdomen and pelvis showed no mediastinal, peritracheal or intra-abdominal involvement. Bone marrow aspiration and biopsy showed hyper cellular marrow, normoblastic erythroid hyperplasia and a marked increase in eosinophils. No abnormal cells were seen. Gross

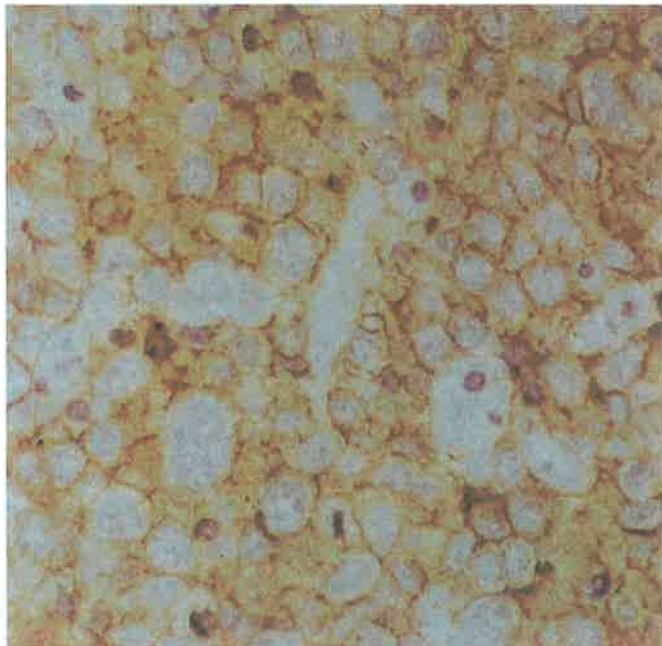
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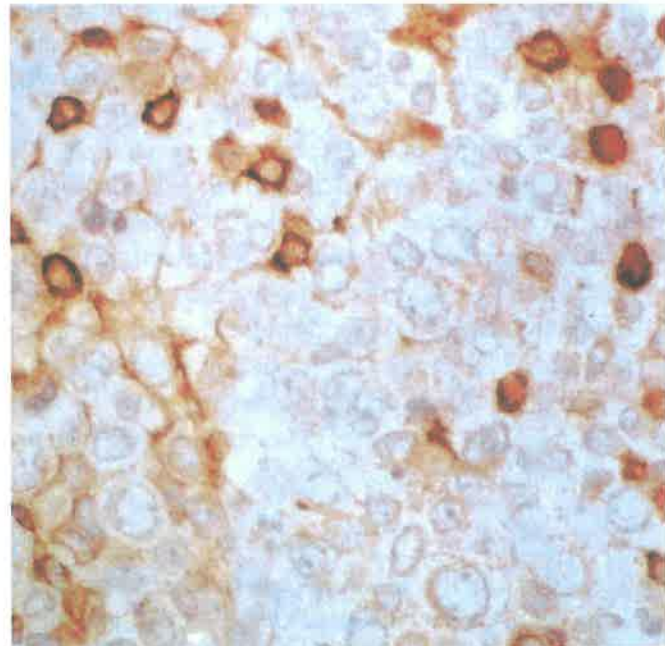
**FIGURE 1.** *Photomicrograph of histological section showing total replacement of salivary gland by islands of malignant tumour cells HE (x250)*



**FIGURE 3.** *Photomicrograph of tumour stained immunochemically showing positive staining of all B cells by CD 20 (x 550)*



**FIGURE 2.** *Photomicrograph of histological section stained by immunocytochemical stain showing leucocyte common antigen positivity of the tumour cells. May (x 550)*



**FIGURE 4.** *Photomicrograph of tumour cells stained immunochemically showing positive staining by Kappa. May (x 550)*

examination of the biopsied swelling showed a single nodular specimen measuring 2.5×1.0×0.5 cm. The cut surface was homogenous, whitish-yellow with hemorrhagic areas. Apart from the routine paraffin sections, a piece of tissue was frozen, for immunocytochemical studies. In-situ hybridisation with biotin labelled DNA probes and electron microscopic study was done for the detection of Epstein-Barr virus. Histological examination revealed no identifiable lymph node tissue. The salivary glands had been almost completely replaced by a monotonous proliferation of small to medium sized tumour cells, which were growing in sheets, with areas of starry-sky pattern and foci of necrosis. Amidst these tumour cells, remnants of salivary gland ducts were seen (figure 1). Immunocytochemical studies revealed the tumour cells to be positive stain of B-cell for LCA (figure 2), CD 20 (figure 3) and Kappa (figure 4). Immunological cell markers were negative for T-cells. For Epstein-Barr virus studies, electron microscopic and DNA in-situ hybridisation tests yielded negative results.

The tumour was classified as a diffuse high grade non-Hodgkins, Burkitt-like lymphoma of the B-cell involving salivary glands.

#### DISCUSSION

The most common abnormal laboratory findings for Hyper IgE syndrome are peripheral eosinophilia and elevated IgE levels. Others include positive *Staphylococcus aureus*-specific IgE antibodies,<sup>9</sup> T-lymphocyte dysfunction<sup>10</sup> and deficiency of suppressor T-cells.<sup>11</sup> Our patient was diagnosed to suffer from immunodeficiency at the age of 3. In spite of being supported by prophylactic antibiotics therapy (initially co-trimexazol and later flucloxacillin, acyclovir, antifungal and regular immunoglobulin infusions), he continued to suffer from frequent bacterial, viral and fungal infections. Antibiotics therapy was based on clinical and microbiological background. The peripheral absolute eosinophil count was repeatedly greater than  $20 \times 10^9/l$  and immunoglobulin E levels were repeatedly above 26.0 KIU/l. *Staphylococcus aureus* specific IgE antibodies were positive.

Four and half years after diagnosis, our patient

developed a diffuse high-grade non-Hodgkin's Burkitt-like lymphoma of the B cell type involving the salivary gland. To our knowledge, while five patients with hyper-IgE syndrome have been reported to develop lymphoid malignancies, there is no report in literature of development of non-Hodgkin's lymphoma in a patient with hyper IgE syndrome. This was probably the first recorded case.

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