Correspondence

Hodgkin's disease and common variable immunodeficiency

We read with interest the paper by Christopoulos *et al.*[1] Several points raised by the authors require comment. In the literature, other cases of Hodgkin's disease complicating primary hypogammaglobulinemia have been reported[2-6] and sometimes in relatives of patients with common variable immunodeficiency (CVID).[7] Another case has been reported recently in a Spanish woman with CVID by Espanol *et al.*[8] Among the 500 cases of cancer in primary immunodeficiency from the Immunodeficiency Cancer Registry, the international database located at the University of Minnesota, 43 cases of Hodgkin's disease have been collected (from 1973 to 1991).[9] Eight cases were reported in association with CVID.[9] We recently reported two cases of Hodgkin's disease complicating IgA and IgG subclass deficiency.[10] There is, possibly, an increased frequency of cancer in this immunodeficiency, as is the case in CVID. IgA deficiency and CVID may represent polar ends of a clinical spectrum, reflecting a common underlying genetic defect.[10]

We disagree with the assertion that CVID is associated with non-Hodgkin's lymphoma, mostly of the T cell type. Of the 55 cases of non-Hodgkin's lymphoma associated with CVID from the Immunodeficiency Cancer Registry, the majority were considered to be of B cell origin on the basis of histological classification or immunophenotyping, or both.[9] The same conclusion can be drawn from the study by Cunningham-Rundles *et al*[11] in 10 patients with non-Hodgkin's lymphoma complicating CVID. These B cell lymphoproliferative disorders in CVID (associated with Epstein-Barr virus?) possibly evolve through distinct stages from polyclonal reactive proliferation to oligoclonal and finally into monoclonal malignant lymphoproliferative syndromes.[9]

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Drs Christopoulos and Kokkini comment:

Dr Zenone's comments focus on two points: the number of reported cases of Hodgkin's disease in patients with CVID and the immunophenotype of non-Hodgkin's lymphoma (NHL) complicating CVID.

According to the criteria of the Immunodeficiency Clinic at the Clinical Research Centre, Northwick Park Hospital, UK, the diagnosis of CVID requires the presence of B cells or onset of symptoms after the age of 5 and persistently low levels of more than one class of immunoglobulin.[1] On this basis, the cases included in Dr Zenone's references 2 to 5 (detailed analysis of which is beyond the scope of this letter), either do not meet the diagnostic criteria for CVID or refer to hypogammaglobulinaemia discovered simultaneously or shortly prior to the diagnosis of Hodgkin's disease; in the latter, the immunodeficiency could in fact have been caused by the lymphoproliferative disorder. In the Newfoundland family reported in reference 7 there were no patients with CVID who developed Hodgkin's disease. The report by Filipovich and Shapiro (reference 9) giving the updated number of Hodgkin's disease entries in the Minnesota Immunodeficiency Cancer Registry was not accessible by Medline when our article was written and, in any case, it does not contain any detailed case reports; the same applies to the Spanish survey reported in reference 8. We acknowledge that Fesus *et al*[2] should probably be credited with the first documented case report of Hodgkin's disease in CVID in the English literature, even though the time interval between verified hypogammaglobulinaemia and onset of Hodgkin's disease in their patient was not clear and four years of prednisone treatment (with the potential of masking the clinical picture) had preceded the diagnosis of the lymphoproliferative disorder. It is nevertheless interesting to note the similarities between their patient and ours: they both presented with extensive extralymphatic disease and showed a similar spectrum of severe, chemotherapy related complications, including possible reactivation of herpesviruses. Our patient was fortunate to survive the treatment and is today well, on monthly immunoglobulin infusions, two years after completion of chemotherapy. Detailed reporting of more of these cases would help to establish patterns of Hodgkin's disease complicating CVID, resulting in earlier diagnosis and more effective treatment. In this context, we welcome the publication by Zenone *et al* of two cases of Hodgkin's disease occurring in a similar immunodeficiency setting.

Regarding the immunophenotype of NHL complicating CVID, nowhere in our report is stated that the majority of these lymphomas are of T cell lineage. In the recent survey by Hermaszewski and Webster[1] eight NHLs were found in 240 British patients with CVID seen over a period of 20 years, the largest single centre series reported so far. These authors state that "to date, all the lymphomas have been undifferentiated or of T cell origin." Given the fact that less than 20% of NHL in the general population are of T cell lineage,[3] our statement that in CVID there is "an apparently high frequency of undifferentiated and T cell tumours" is justified.

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Frequency of coincident iron deficiency and β-thalassaemia trait

We read with interest the paper by Hinchliffe *et al*[1] describing coincident iron deficiency and β-thalassaemia trait. β-thalassaemia is the commonest haemoglobinopathy in India.[2] We investigated 463 patients heterozygous for β-thalassaemia trait, 88 (19%) of whom were children. Of these 463 patients, 126 (27.2%) had iron deficiency, 33 (26.2) of whom were children. Of 195 iron deficient subjects without β-thalassaemia trait, 116 (59.5%) were children. Of these, 75.9% were under five years of age.

Seventy two per cent of patients with β-thalassaemia trait but without iron deficiency were anaemic compared with 90.4% of those with β-thalassaemia trait and coincident iron deficiency. This difference was highly significant ($p < 0.001$). The mean (SD) haemoglobin concentration was significantly lower in the latter (10.7 (1.5) g/dl) than in the former patients (11.6 (1.6) g/dl), as were the mean cell haemoglobin and the mean corpuscular volume ($p < 0.0001$).

Mean (SD) HbA_2 was 5.11 (0.8)% in patients with β-thalassaemia trait with iron deficiency and 5.19 (0.73)% in those without (NS). Mean (SD) HbA_2/cell was 1.002 (0.207) pg in the former and 1.069 (0.248) pg in the latter. This difference was significant ($p < 0.05$).

We agree with Hinchliffe *et al* that iron deficiency occurs with a high frequency in children under five years of age and that any advantage in iron supply conferred by β-thalassaemia trait does not protect against iron deficiency in either adults or children. In our study, HbA_2 concentrations were increased in all patients, irrespective of their iron status, and did not preclude the detection of the heterozygous state.

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