Hodgkin’s disease and common variable immunodeficiency

We read with interest the paper by Chris-
topoulou et al. Several points raised by the authors require comment. In the literature, other cases of Hodgkin’s disease complicating primary hypogammaglobulinemia have been reported and sometimes in relatives of patients with common variable immunodefi-
ciency (CVID).1 Another case has been reported recently in a Spanish woman with CVID by Espanol et al.2 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).3 Eight cases were reported in association with CVID.4 We recently reported two cases of Hodgkin’s disease complicating IgA and IgG subclass deficiency.5 There is, however, an increased frequency of cancer in this group of patients.6 It is therefore appropriate to review the cases of CVID. IgA deficiency and CVID may repre-
sent polar ends of a clinical spectrum, reflect-
ing a common underlying genetic defect.7

We disagree with the statement that CVID is a late complication of 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 histologic classification or immunophenotypic analysis.8 The same conclusion can be drawn from the study by Cunningham-Rundles et al.9 in 10 patients with non-Hodgkin’s lymphoma complicating CVID. These B cell lymphoproliferative disorders in CVID (asso-
ciated with Epstein-Barr virus?) possibly evolve through distinct stages from polyclonal reactive proliferation to oligoclonal and finally into monoclonal malignant lympho-
proliferative syndromes.10

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3 Gellman EF, Vietti TJ. Congenital hypogamma-
5 Li G, Hansmann ML. Lymphocyte predomi-
nant Hodgkin’s disease of nodular subtype complicating a primary lymphoid prolifer-
6 Fesus SM, Hamegeimer FB, Manning J, Hodg-
11 Cunningham-Rundles C, Lieberman P, Hell-

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 diagnostic immunophenotype of non-Hodgkin’s lymphoma (NHL) complicating CVID.

According to the criteria of the Immunode-
fi ciency Clinic at the Clinical Research Cen-
tre, Northwick Park Hospital, UK, the diagnosis of CVID requires the presence of B cells or onset of symptoms at the age of 5 and persistently low levels of more than one class of immunoglobulin.1 On this basis, the cases included in the Zenone et al. report (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 simul-
taneously or shortly prior to the diagnosis of Hodgkin’s disease; in the latter, the immuno-
deficiency 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 Filippovich 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 sur-
vey reported in reference 8. We acknowledge that Fesus et al. could probably be credited with the first documented case of report of Hodgkin’s disease in CVID in the English liter-
ature, even though the time interval be-

tween verified hypogammaglobulinaemia and onset of Hodgkin’s disease in their patient was not clear. Our patient was fortunate to receive treatment (with the potential of masking the clinical picture) that 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 receive effective treatment and is today well, on monthly immunoglobulin infusions, two years after completion of chemotherapy. Detailed re-
porting of more of these cases would help to establish patterns of Hodgkin’s disease com-
paring 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.

Regardless of 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 et al.10 on NHL, 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,1 our statement that in CVID there is “an apparently high frequency of undifferen-
tiated and T cell tumours” is justified.

2 Fesus SM, Hamegeimer FB, Manning J. Hodg-
3 Freedman AS, Walder LM. Immunologic mark-

Frequency of coincident iron deficiency and β-thalassaemia trait

We wish to echo the concern by Hinchliffe et al. describing coincident iron deficiency and β-thalassaemia trait. β-thalassaemia is the commonest haemoglobinopathy in India.2 We investigated 436 patients hetero-
ygous for β-thalassaemia trait, 89 (19%) of whom were children. Of these, 102 (26.7%) 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 defi-
ciency were anaemic compared with 90.4% of those with β-thalassaemia trait and coinci-
dent iron deficiency. This difference was highly significant (p < 0.001). The mean (SD) haemoglobin concentration was signifi-
cantly 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) HbA2 was 5.11 (0.8%) in patients with β-thalassaemia trait and 5.19 (0.73%) in those without (NS). Mean (SD) HbA2-cell was 1.002 (0.207) g/dl in the former and 1.069 (0.248) g/dl in the latter. This difference was signifi-
cant (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, HbA2 concentrations were in-
creased in all patients, irrespective of their iron status, and did not preclude the detection of the heterozygote.

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1 Hinchliffe RF, Lilleyman JS. Frequency of coinci-
2 Sukumar PK. Abnormal haemoglobins in India. In: Sen NN, Basu AK, eds. Trends in haem-