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Drs Williamson et al comment:

The case cited above is certainly of interest in investigating the pathogenesis of red cell aplasia in myelodysplasia (MDS). The overlap of morphological features between MDS and myelofibrosis is increasingly being recognised,¹ and it would be intriguing to know the consequences at the gene level in this case of 11q- with break point at 11q13.

Our cases all had attempted cytogenetic analysis of marrow aspirate. Four gave a normal karyotype and two failed to yield metaphases. Several of our cases date from the early 1980s and the cytogenetic technique has undoubtedly improved since then. Our rate of clonal cytogenetic abnormality in MDS in the Wessex region is about 35-40% which accords with the national average. A few published series quote clonal abnormality rates of 75% plus, but these may be the result of repeated analysis of large numbers of cells and may be influenced by case selection. In the Wessex region we have never encountered the 11q13 region as being involved in a case of MDS. The 1988 Catalogue of Chromosomal Aberrations in Cancer² lists only five reported cases where the 11q13 region has been involved in myelodysplastic/proliferative disorders, often as part of a complex karyotype. A review of the other published cases of MDS and red cell aplasia referenced in our paper shows that all five in which cytogenetics are reported yielded a normal karyotype. Thus although of some interest, it remains to be seen if the 11q13 region has a role in the regulation of erythropoiesis.

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Visceral leishmaniasis in human immunodeficiency virus disease

I read the very interesting article by Curry, Turner, and Lucas.¹ It is important to include visceral leishmaniasis (VL) as an opportunistic protozoan infection in patients infected with HIV, as it is common in endemic areas.² Although the authors comment on some of the salient diagnostic and therapeutic features of VL in patients with HIV, the description is perhaps incomplete as it is based on only a few cases. Over the past few years, most cases of VL in HIV infection have been reported from Spain, probably due to a high incidence of

both VL and HIV infection and a greater awareness about this association once the first few cases had been described. In 1990 two independent studies described the features of VL in many cases of HIV.^{2,3} More recently, our cooperative multicentre study of 40 patients, including most cases that had appeared in Spain up to the beginning of 1990, has updated that experience.⁴

Although in some patients VL can be the consequence of reactivated disease, the finding that 92.5% of the patients were intravenous drug misusers suggested that the disease could be transmitted intravenously (which is an occasional route of transmission in immunocompetents). VL can occur at all stages of HIV infection, but 77% of patients were classified as stage IV with CD4 counts below $4 \times 10^9/l$, suggesting that it is commoner in the later stages of HIV infection. Most patients present with a clinical picture of "classic" Kala-azar with fever, hepatosplenomegaly, and pancytopenia, but some are asymptomatic and are diagnosed incidentally. In all patients *Leishmania amastigotes* were demonstrated in the bone marrow smear, and in the liver of 94.5% of the patients who had a biopsy. In four cases *L. amastigotes* were found in normal skin, and were also present in skin lesions of a Kaposi's sarcoma in one case. This is not a surprising finding, as *L. amastigotes* are found in normal skin in immunocompetent patients with VL. The two most remarkable findings were the absence of leishmanial antibodies, present in only 35.2% of cases, and the chronic relapsing course of the disease. Although 75% of patients had a good initial response to antimony drugs, 42.5% followed a chronic or relapsing course; 40% of patients died due to HIV related causes, and death was only inadvertently related to the relapsing course of the disease.

These findings suggest that VL behaves like other infections in HIV seropositive patients, such as tuberculosis or *Pneumocystis carinii*, showing a good response to initial treatment but persisting as latent chronic disease. Conventional treatment with antimony is not effective in half the patients and other therapeutic approaches are needed. Production of α -interferon (α -INF) and other lymphokines are essential to activate macrophages, but these are defective in both VL and HIV infections. Adjuvant treatment with γ -INF has been effective in animals, in experimental models of human macrophages, and in refractory VL in immunocompetent patients.⁵ These results suggest that γ -INF could also be effective in VL in HIV seropositive patients and a therapeutic trial is currently being conducted in Spain.

VL is an opportunistic infection in HIV seropositive patients that is found increasingly often. It must be suspected and precluded in patients presenting with fever, hepatosplenomegaly, and pancytopenia, and even in less ill patients living in or travelling to endemic areas.

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- 1 Curry A, Turner AJ, Lucas S. Opportunistic protozoan infections in human immunodeficiency virus disease: Review highlighting diagnostic and therapeutic aspects. *J Clin Pathol* 1991;44:182-93.

Defective erythropoiesis in myelodysplastic syndromes

We read with interest the report of Williamson et al describing uncommon cases of red cell aplasia (RCA) in patients with myelodysplastic syndromes (MDS).¹ The mechanism of RCA in their first three cases was attributed to an intrinsic defect of maturation and proliferation of erythroid precursors occurring as part of the myelodysplastic disorder, whereas in the second three cases a different, and possibly autoimmune aetiology, was suggested. We believe that cytogenetic and molecular study of such unusual cases is important. Most cases of MDS and other malignant haematological disorders are associated with structural chromosomal abnormalities. Cytogenetic study of unusual cases with common features, such as these cases of RCA, might indicate a common chromosomal abnormality which would point to the existence of genes which encode key regulators of erythroid lineage development at or near the junction of the chromosomal aberration. The key regulators of lineage commitment and differentiation in haemopoiesis remain unknown, and an investigative approach through the study of nature's genetic errors might lead to their discovery.

Using such an approach we have recently described a possible association between defective erythropoiesis and an abnormality of chromosome 11.² A case of primary myelofibrosis was identified which showed morphological erythroid aplasia and absent circulating erythroid progenitors. The patient had greatly increased numbers of circulating granulocyte-monocyte progenitor cells (CFU-GM). Co-culture of peripheral blood mononuclear cells with irradiated allogeneic normal bone marrow stroma generated increased numbers of CFU-GM compared with controls but failed to generate erythroid progenitors, providing further evidence for an intrinsic defect in erythropoiesis. Our patient exhibited a previously unreported complex karyotype. Only once previously has the absence of erythroid progenitors in primary myelofibrosis been studied in relation to cytogenetic abnormalities, and this case also indicated a complex karyotype which shared with our case a defect on chromosome 11. The abnormality in our case was 11q- with the break point at 11q13. A literature review showed that the proto-oncogene SEA (S13 avian erythroblastosis oncogene homolog) maps to the 11q13 region and we intend to study the possible role of this gene at the molecular level.