Unusual Cases of Myelomatosis

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We have recently seen four patients with myelomatosis which terminated as acute leukaemia.

The first was a 62-year-old woman who died three and a half years after the diagnosis of myelomatosis and after being treated with melphalan for a little over three years. In the last six weeks of life the white cell count suddenly increased to reach 120,000/mm³. The cells were predominantly myeloblasts, and the bone marrow contained about 75% of blast-like cells which had not apparently been there before; often the myeloblasts and myeloma cells were seen side by side. In the second patient myelomatosis was diagnosed nearly two years before death. Initially she was treated with *x*-irradiation and melphalan was given for 16 months. In the last four weeks of life the picture changed: the white cell count rose to 136,000/mm³ with 88% blasts, and the bone marrow contained 96% of the same type of cells.

The diagnosis of myelomatosis was made in the next patient four and a half years before death, and he had received either melphalan or cyclophosphamide for the whole of the period. One day before death the white cell count was only 4,060/mm³ but the buffy coat contained many typical blast cells, which we were unable to classify further. In the fourth patient myelomatosis was diagnosed more than six years before death. She was treated with cyclophosphamide for five and a half years, when it was stopped because of leucopenia. During the following months her leucocyte count rose to 14,000/mm³ and an increasing number of blasts appeared in the peripheral blood. The predominant cell in the bone marrow was a stem cell, again distinctly different from the myeloma cells.

These four typical cases of the development of acute leukaemia were seen among 19 consecutive patients with myelomatosis in our clinic; they were not considered as cases of plasma cell leukaemia because morphologically the blast cells in the blood and bone marrow could not be characterized as myeloma cells.

Some other cases may now be mentioned.

A man treated for three years with 5-10 mg prednisone and 1-2 mg melphalan daily had an M-component amounting to 9 g/100 ml at diagnosis, though later this decreased considerably. Subsequently, thrombocytopenia and anaemia developed, and the erythrocyte sedimentation rate, which for a long time had been nearly normal, increased simultaneously with a rise in the M-component. In the last two weeks of life the white cell count increased to about 50,000/mm³, with many blasts, and the bone marrow contained 80% stem cells, which we believed were most probably myelomonocytic.

The sixth case, a 52-year-old woman, developed severe generalized pain. Investigations showed a very high erythrocyte sedimentation rate, an increased serum total protein, a high serum M-component of the gamma-G type, and heavy Bence Jones proteinuria. Radiologically there was also a soap-bubble appearance and a fracture in one of the ribs. One month later epistaxis occurred and a month after this severe anaemia and thrombocytopenia were found together with many blasts in the peripheral blood; the bone marrow was hypercellular and contained many stem cells, probably myeloblasts. At necropsy, four months after her symptoms, stem cell infiltrations were found at several sites, particularly the pleura, where numerous whitish infiltrates from a few millimetres to 1 cm in diameter were seen. No metastasizing solid tumour was found. From the beginning the diagnosis was aleukaemia myeloblastic leukaemia and myelometosis because she showed simultaneously a monoclonal gamma-G component, Bence Jones proteinuria, bone changes, and myeloma cells in the bone marrow. Even so, when the bone marrow smears were treated with fluorescein-labelled anti-IgG the blast cells showed intense cytoplasmic fluorescence, as did the myeloma cells.

Two conclusions may be drawn from this last case history. Firstly, if the diagnosis here is the simultaneous occurrence of acute leukaemia and myelomatosis (as in the five other patients) no previous treatment with cytotoxic drugs is necessary to produce this combination of diseases. Secondly, the fluorescent studies show how difficult it is to make a diagnosis on morphological grounds because most of the cells considered to be stem cells were shown to behave like myeloma cells. It will be interesting to see in future cases whether the stem cells really are myeloma cells merely completely changed in appearance or whether they represent a new cell line.

I should now like to describe a case of macroglobulinaemia in which stem cell leukaemia developed.

This was a 78-year-old woman admitted for investigation of anaemia (a haemolgobin level of 9 g/100 ml). On investigation thrombocytopenia and a white cell count of 17,600/mm³ with 80% of lymphocytes were found. The bone marrow contained 90% of lymphocyte-like cells and a few plasma cells. The serum contained a high concentration of a M-component, which immunoelectrophoresis showed was gamma-M protein; ultra-centrifugation revealed a high S_{16} component and a slightly increased S_{24} component was seen. The urine contained a high concentration of Bence Jones protein and hence an unequivocal diagnosis of Waldenstroms macroglobulinaemia was made. Nevertheless, in a few weeks the picture changed, with the appearance of blasts in the blood and the bone marrow. The very short course of chlorambucil is unlikely to have caused this development. Possibly the two conditions occurred together by coincidence or the leukaemia was the primary disease and the monoclonal gammopathy of the IgM-type was a subsequent development.

Thus to the many conditions which may precede acute leukaemia I think we must add possibly also Waldenstroms macroglobulinaemia. We still do not know whether the supervention of acute leukaemia, which is the rule in chronic myeloid leukaemia and rare in untreated polycythaemia vera, is part of the natural history of these diseases. Might this development occur spontaneously and be accelerated by cytostatics, *x*-irradiation, and ^{32}P? Is the leukaemia due to the growth of a new clone, different from that responsible for the gammopathy or has the myeloma alone changed its degree of differentiation? Is the decrease of concentration of the M-component in serum due to a reduction of the myeloma cell clone or has the cytostatic treatment changed the secretion power of the myeloma cells and thus the degree of differentiation?

If acute leukaemia is drug-induced or drug-accelerated, this suggests that the reaction is peculiar to myelomatosis and the related diseases. After all, cyclophosphamide has been used for many patients—for example, in those with Hodgkin's disease—without leading to acute leukaemia. The final question is whether the products secreted by the myeloma cells represent antibodies, and if so to what antigen. There is a slowly growing number of published cases of monoclonal gammopathy where the M-component has shown immunological specificity, though only a few of these were patients with myelomatosis. We have now seen four patients of monoclonal gammopathy with so-called immunological specificity; the first two patients had typical myelomatosis. The serum of the first patient contained an M-component of 5 g/100 ml of the gamma-G type, while the anti-α-staphylolysin titre was extremely high (6·400 units/ml). In the second patient there was a monoclonal gamma-A component, type kappa, in the serum starting at a level of 2·4 g/100 ml; this had a specificity of ASO (antistreptolysin O) with a titre of 5½ million units.

Nevertheless, though these two and other reported cases of myelomatosis with apparently specific M-components have had this unusual feature of immunological specificity, in every other way the features of the disease have been no different from that of conventional myelomatosis.

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