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## When is the 'idiopathic' hypereosinophilic syndrome eosinophilic leukaemia?

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The diagnosis of idiopathic hypereosinophilic syndrome is one of exclusion, requiring significant unexplained eosinophilia which persists for at least 6 months and is associated with tissue damage. The relationship of this condition to eosinophilic leukaemia remains controversial. In some patients who present with hypereosinophilia and damage to the heart and other tissues the condition can be shown to be reactive. In others a diagnosis of eosinophilic leukaemia can be made when an increase of blast cells or a clonal cytogenetic abnormality is detected. Other cases which fit the definition of idiopathic hypereosinophilic syndrome can be recognized in retrospect as eosinophilic leukaemia when there is subsequently development of a clonal cytogenetic abnormality or of acute myeloblastic leukaemia or granulocytic sarcoma. In a small number of patients other mechanisms of eosinophilia have been demonstrated with secretion of cytokines by T cells, sometimes a clonal population of T cell, being demonstrated.

Chronic eosinophilic leukaemia has been associated with a number of cytogenetic abnormalities including trisomy 8, isochromosome 17q, monosomy 7 and t(5;12)(q31-q33;p12-13). The most specific association is with t(5;12). Cytogenetic analysis is recommended in cases of unexplained eosinophilia.

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The nature of the idiopathic hypereosinophilic syndrome (idiopathic HES) remains uncertain and its relationship to eosinophilic leukaemia is controversial. The diagnosis is one of exclusion. Idiopathic HES has been defined as an eosinophil count in excess of  $1.5 \times 10^9/l$ , persisting for at least six months which is associated with tissue damage (such as cardiac damage and intracardiac thrombosis) and is unexplained (1).

With appropriate investigation and an adequate period of follow up most cases of reactive eosinophilia can be distinguished from the idiopathic hypereosinophilic syndrome. However the distinction of eosinophilic leukaemia, defined as a neoplastic condition with marked or predominant eosinophilic differentiation, from idiopathic HES is not always possible.

Equally high eosinophil counts and cardiac and other tissue damage as a consequence of release of eosinophil granule contents can occur in eosinophilic leukaemia, reactive eosinophilia and idiopathic HES. Similarly, morphological abnormalities of eosinophils - such as vacuolation and hypogranularity, hyper and hyposegmentation and ring nuclei - can occur in all these categories of disease. Other criteria are needed to make the distinction. A diagnosis of eosinophilic leukaemia can be made when there is an increase of blast cells, when a clonal cytogenetic abnormality is demonstrable or when there is other evidence of clonality such as skewed expression of G6PD or other X chromosome genes or mutation of an oncogene (table 1).

### The significance of eosinophilia in myeloproliferative disorders

Since the eosinophil is derived from the multipotent haemopoietic stem cell it is not unexpected that eosinophilia occurs in some myeloproliferative diseases. 80 to 90% of cases of Ph-positive chronic granulo-

**Table 1.** Criteria for making a diagnosis of chronic eosinophilic leukaemia

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Blast cells are increased but are less than 30% of bone marrow cells.

There are clinical and haematological features indicative of leukaemia such as hepatomegaly, splenomegaly, anaemia and thrombocytopenia.

Eosinophils can be demonstrated to be clonal by investigation of X-linked polymorphism or by detection of a clonal oncogene mutation or cytogenetic abnormality.

A clonal cytogenetic abnormality subsequently develops or granulocytic sarcoma or acute myeloid leukaemia develops (retrospective diagnosis of chronic eosinophilic leukaemia is possible).

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cytic leukaemia have peripheral blood eosinophilia and a higher percentage have an increase of eosinophils and their precursors in the bone marrow. The eosinophils have been demonstrated to be part of the neoplastic clone. It is likely that the eosinophils are also clonal in the smaller percentage of cases of polycythaemia rubra vera, essential thrombocythaemia and idiopathic myelofibrosis with eosinophilia. About a quarter of cases of systemic mastocytosis also have eosinophilia and a minority of patients have very high counts with features similar to those of idiopathic HES (2,3). Mast cells are derived from the multipotent haemopoietic stem cell and it is likely that most, if not all, cases of systemic mastocytosis represent a myeloproliferative disease. However it has not yet been established whether the eosinophils are part of a neoplastic clone or whether eosinophil differentiation is consequent on secretion of IL5 and other cytokines by mast cells.

#### **When is 'idiopathic' hypereosinophilia actually eosinophilic leukaemia?**

In addition to patients with eosinophilia in association with recognized myeloproliferative disorders there are others with predominant eosinophilic proliferation where the differential diagnosis is between eosinophilic leukaemia and idiopathic HES. Cases which are found to have a clonal cytogenetic abnormality should be classified as eosinophilic leukaemia rather than as idiopathic HES. Sometimes the karyotypic abnormality is one such as trisomy 8 or isochromosome 17q which is found in a variety of myeloid malignancies. Sometimes a Philadelphia chromosome is demonstrated and such cases are best regarded as variants of chronic granulocytic leukaemia.

Most reports of Philadelphia-positive eosinophilic leukaemia date from the prebanding era of cytogenetics and the typical 9;22 translocation was not recognized. However cases with the typical translocation associated with hypereosinophilia and marked cardiac damage have been described (4). An uncommon cytogenetic abnormality which is strongly associated with a myeloproliferative disorder with prominent

eosinophilic differentiation is t(5;12)(q31-q33; p12-13). The majority of reported cases have had eosinophilia (with counts as high as  $128 \times 10^9/l$ ) and some have had tissue damage attributable to hypereosinophilia. Some patients have also had anaemia or thrombocytopenia, neutrophilia, monocytosis or trilineage myelodysplasia. The eosinophils have been demonstrated to be part of the abnormal clone (5). It has been postulated that the eosinophilic differentiation associated with t(5;12) is related to the location of the IL5 gene and other cytokine genes at or near the 5q breakpoint. However analysis of two cases with t(5;12)(q31;p12) (in which eosinophilia was not mentioned) demonstrated that the IL3 and IL5 genes were not rearranged (6). In another case with t(5;12)(q33;p13), characterized as chronic myelomonocytic leukaemia (without any mention of eosinophilia), an alternative molecular mechanism of leukaemogenesis was shown (7). There was fusion of the tyrosine kinase domain of the gene for platelet derived growth factor receptor  $\beta$  (PDGFR $\beta$ ) at 5q33 with part of TEL, a novel gene of the ETS family, at 12p13. The fusion gene was expressed. A further five cases of chronic eosinophilic leukaemia or myeloproliferative or myelodysplastic disorders with prominent eosinophilic differentiation have been associated with other translocations with 5q31-35 breakpoints. Two such cases were associated with t(5;12)(q31;q13), i.e. with a breakpoint on the long rather than the short arm of chromosome 12 (8,9), two with t(1;5)(q23;q33) (10) and one with t(2;5)(p23;q35) (11). It appears likely that genes located between 5q31 and 5q35 are important in the causation of leukaemia with eosinophilic differentiation. These could include genes for PDGFR $\beta$  and for cytokines including IL3, IL4, IL5, IL9 and GM-CSF. Individual cases of eosinophilic leukaemia have also been associated with a variety of miscellaneous cytogenetic abnormalities including monosomy 7, trisomy 10, 17q+, 15q-, t(7;12)(q11;p11), t(4;6)(q11 or 12;p13) and complex cytogenetic abnormalities.

In some patients with eosinophilia, with or without a clonal cytogenetic abnormality, a diagnosis of eosinophilic leukaemia can be made on the basis of a significant increase in blast cells in the bone marrow. In other cases which are cytogenetically normal and have no increase of blast cells a presumptive diagnosis of eosinophilic leukaemia can reasonably be made on the basis of clinical and haematological features such as hepatosplenomegaly, anaemia and thrombocytopenia which are otherwise unexplained (12).

After cases of eosinophilic leukaemia have been diagnosed on the above criteria there remain cases initially categorized as idiopathic HES which can be diagnosed as eosinophilic leukaemia in retrospect. In such cases there is subsequently development of a clonal cytogenetic abnormality, a granulocytic sarcoma or overt acute myeloid leukaemia indicating that the initial disorder was myeloproliferative or leukaemic in nature with subsequent acute transformation having occurred.

### Is the 'idiopathic' hypereosinophilic syndrome always a myeloproliferative disorder?

Although some cases with eosinophilia which is initially 'idiopathic' can be shown either on further investigation or by the subsequent course of the disease to have a myeloproliferative disorder this is not always so and other pathogenetic mechanisms have been demonstrated. Individual cases of idiopathic HES have been reported with an abnormal clone of T cells secreting IL4 and IL5 (13) and with peripheral blood T cells colonies secreting an eosinophil colony stimulating factor (14). In three further cases an elevated serum concentration of IL5 was demonstrated (15).

### Conclusion

The haematological disorder in patients with hypereosinophilia who are found to have a cytogenetic abnormality, an increased percentage of blast cells or clinical and haematological features strongly suggestive of leukaemia should not be categorized as 'idiopathic' HES since the nature of the disorder is known or strongly suspected. The correct diagnosis is eosinophilic leukaemia. In a further group of patients the 'idiopathic' hypereosinophilic syndrome can be diagnosed as eosinophilic leukaemia only in retrospect. In other cases the underlying cause of hypereosinophilia remains unexplained at the time of death or an alternative mechanism for eosinophilia is demonstrable.

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