

Cancer Prone Disease Section

Mini Review

Congenital neutropenia

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Identity

Alias

Severe chronic neutropenia (SCN)
Kostmann syndrome

Note

Severe chronic neutropenia is a general term that applies to both congenital and acquired cases. Kostmann syndrome is a subtype of chronic neutropenia with onset in early childhood with an autosomal recessive pattern of development. The term congenital neutropenia is used interchangeably although some authors argue that the term is more appropriate for sporadic cases.

Clinics

Note

Severe chronic neutropenia (SCN) is a heterogeneous group of disorders characterized by chronic neutropenia and serious recurrent infections. The defining characteristic of all of these diseases is the presence of severe neutropenia with absolute neutrophil counts of less than $0.5 \times 10^9 / L$ on three separate occasions over a six week period. Some clinically distinctive cases, known as cyclic neutropenia show oscillation in neutrophil levels with a periodicity of approximately 21 days. SCN is distinguished from Shwachman-Diamond Syndrome by the absence of exocrine pancreas deficiency and growth retardation.

Phenotype and clinics

Phenotype stem cell origin: Constitutional disorder affecting myeloid lineage cells.

Epidemiology: The disease is most common in caucasians and presents in childhood.

Clinical features: Congenital neutropenia usually presents in early childhood and is slightly more

common in males. Cyclic forms are slightly more common in females. SCN patients develop frequent fevers, skin infections and stomatitis with organisms such as *E. coli*, *S. aureus*, and *Pseudomonas* species. 90% of patients are diagnosed by 6 months of age. Patients tend to develop hematological malignancies (see below).

Pathology: The absolute neutrophil count is usually less than $0.2 \times 10^9 / L$. The bone marrow of affected patients shows an arrest in maturation at the promyelocyte stage, often with a monocytosis and sometimes with eosinophilia. The peripheral blood shows a paucity of neutrophils and often monocytosis and eosinophilia.

Neoplastic risk

Roughly 50% of patients present with myelodysplastic syndromes (MDS), another 10% with therapy associated MDS, 25% with de novo acute myeloid leukemia (AML), and the remainder with a range of other myeloproliferative disorders. The majority of MDS patients transform into AML with a short preleukemic phase.

Treatment

More than 90% of patients respond to G-CSF therapy, which may result in cyclic oscillations in neutrophil count. G-CSF therapy may be complicated by significant bone loss and the development of AML. Hematopoietic stem cell transplantation has shown promise in the treatment of non-responders.

Prognosis

With the advent of G-CSF therapy infectious deaths are rare. Approximately 10% of patients develop AML. This is associated in almost all cases with G-CSF-R mutations. This is not thought to be the direct result of G-CSF therapy but rather an underlying predisposition for the development of myeloid leukemia. Cyclic

neutropenia patients do not have an increased risk for development of acute leukemia.

Cytogenetics

Inborn conditions

The majority of patients have point mutations involving neutrophil elastase located at chromosome 19p13.3.

Cytogenetics of cancer

Cases complicated by the development of AML most commonly show monosomy 7 or trisomy 21. Activating RAS mutations are seen in roughly 50% of secondary AML cases.

Genes involved and proteins

Note

Most patients show point mutations in ELA2, a protein that is present in azurophilic granules. In one series of 22 patients 17 different mutations were identified. Most of these were missense mutations. The association between defects in the serine protease ELA2 and neutropenia is thought to involve shortened myeloid progenitor survival. The mechanism of this is obscure. This does not appear to be either loss of function or gain of function (i.e. through cytotoxicity). The evidence to date best supports a dominant negative mechanism whereby the activity of the wild type protein is inhibited. One report suggested that mutation of ELA2 alone was not sufficient for the neutropenia phenotype. It is noteworthy in this regard that mice with knockout of ELA2 show disorders in neutrophil function but not neutropenia.

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