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Review

Primary immunodeficiencies appearing as combined lymphopenia, neutropenia, and monocytopenia

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ABSTRACT

Recurrent or prolonged severe infections associated to panleukopenia strongly suggest primary immune disorders. In recent years, new immunodeficiency syndromes turned up: besides the importance of continuous clinical characterization throughout added reports, the phenotype can easily lead to diagnosis of known rare entities. Our purpose is to review main emerging genetic syndromes featuring lymphopenia combined to neutropenia and/or monocytopenia in order to facilitate diagnosis of rare primary immune deficiencies.

1. Introduction

Primary immunodeficiencies comprise more than 180 inherited disorders that affect the development and functions of lymphocytes, neutrophils or monocytes [1]. They constitute a challenging group of diseases for the clinician because of the low incidence of these diseases and for the little knowledge of general practitioners and pediatricians with these disorders. Because of that, the time that elapses between the appearance of the first clinical manifestation and the time of confirmed diagnosis is quite long in many cases. In addition, primary immunodeficiencies constitute an heterogeneous group of diseases with broad variations in the clinical phenotype. While severe combined immunodeficiencies are usually identified within the first year of life, other primary immunodeficiencies with less complex phenotypes can be more difficult to be recognized until invasive infections sustained by bacterial, viral or fungal pathogens become evident in the first or second decade. In the last years, we have assisted at an increasing interest of biomedical researchers in the identification of the genetic and immunological features of primary immunodeficiencies appearing late in infancy with specific alterations of leukocyte blood count. In this review article, we will focus on the primary immunodeficiencies that are characterized by a combined defect of both lymphocyte and myeloid lineages that result in lymphopenia associated with neutropenia or monocytopenia while hemoglobin and platelet levels are normal. Moreover, investigation of the genetic basis of this group of disorders of hematopoiesis has provided novel insights in the knowledge of normal lymphoid and myeloid development (Fig. 1 and Table 1).

2. WHIM syndrome

CX chemokine receptor 4 (CXCR4)-dependent syndrome is the first described human chemokine receptor disorder primarily known as WHIM syndrome [2], as the typical phenotype includes recurrent bacterial infections, cutaneous warts, hypogammaglobulinemia, and myelokathexis. Autosomal dominant mutations affect from 10 to 19 amino acids of the cytosolic carboxy-terminal tail of CXCR4; C-tail truncation of the chemokine receptor results in enhanced and prolonged response to the unique ligand CXCL12, whose expression is predominant in bone marrow. CXCR4 is expressed by hematopoietic cells and many stem and progenitor cells, highlighting the role of CXCR4/CXCL12 interaction in regulating bone marrow homeostasis, hematopoiesis and leukocyte trafficking among lymphoid organs. In addition, CXCR4 is also involved in organogenesis, vascularisation, and cancer development.

WHIM syndrome is characterized by broad clinical heterogeneity [3]. However, all patients have a history of recurrent bacterial infections, mainly pyogenic infections since early childhood, but severity and frequency of infectious episodes is very variable from case to case. Long term complications, particularly chronic

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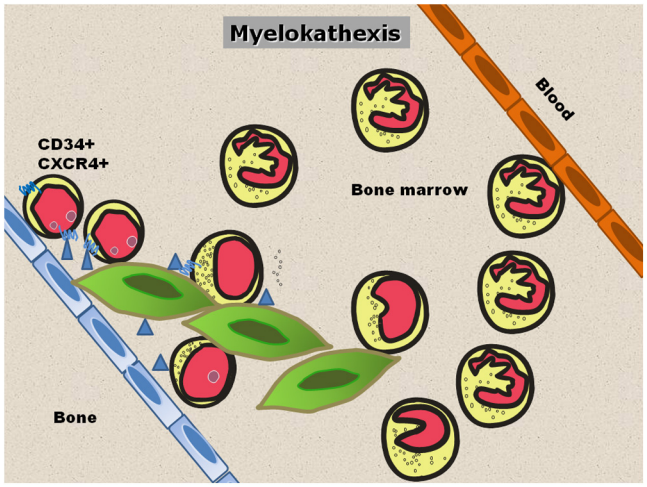

Fig. 1. *Mechanism of neutropenia in patients with myelokathexis*. Bone marrow is characterized by presence of an abundant number of hypermature neutrophils despite the observation of neutropenia in peripheral blood. In WHIM patients, truncation of the intracellular tail of CXCR4 (shown as seven transmembrane receptor) results in increased response of the chemokine receptor to the ligand CXCL12 (shown as blue triangle) secreted by stromal cells in bone marrow. Despite myeloid differentiation is associated with a sensible decline in the expression of CXCR4, mature neutrophils are retained in the bone marrow of WHIM patients because of the increased sensitivity of these cells to CXCL12. Myelokathexis has been also described in sporadic cases of G6PC3 deficiency.

obstructive pulmonary disease and bronchiectasis are rare, but have been described in a limited number of patients suffering from repeated respiratory infections [4]. Interestingly, three patients diagnosed as WHIM manifested tetralogy of Fallot, remarking the role of CXCR4/CXCL12 axis, and probably of CXCR7, in valve morphogenesis during heart development [5]. Susceptibility to human papilloma virus (HPV) infection is a typical sign of the disease, even though cutaneous warts affect only the 70% of WHIM patients and usually appear in the second decade of life. Typically, HPV-infections observed in WHIM patients are refractory to conventional medical and surgical treatments and are associated with higher risk of HPV-related genital dysplasia and cancer, representing the main cause of death in WHIM patients. EBV-related B-cell lymphoma has been described. All WHIM patients present neutropenia, associated to monocytopenia and B and T cell lymphopenia [3,4]. In details, lymphocyte deficiency affects memory B cells and naïve T cells. Bone marrow features myelokathexis, as abnormal retention of senescent neutrophils resulting from the mutated-CXCR4 gain of function (Figure 1). Despite WHIM patients present severe neutropenia and lymphopenia, they may survive severe infections because bone marrow is still able to release retained neutrophils to blood circulation during infectious episodes. Hypogammaglobulinemia is variable and typically intermittent because immune response against antigens is preserved. Bacterial infections promptly respond to antibiotic therapy. Granulocyte-Colony Stimulating Factor (G-CSF) is used to normalize neutrophil count, while treatment with intravenous immunoglobulin is used in patients with hypogammaglobulinemia. But, recent trials experimenting the use of the CXCR4 antagonist plerixafor in patients with WHIM syndrome have shown promising results, as this therapy was effective to durably reverse panleukopenia, to reduce frequency and severity of infections [6,7].

3. G6PC3 deficiency

Autosomal recessive glucose-6-phosphatase catalytic subunit three (G6PC3) deficiency is a newly described type of severe congenital neutropenia (SCN) with an heterogeneous and complex phenotype [8]. G6PC3 is a ubiquitously expressed enzyme that is essential in the final step of gluconeogenesis and glycogenolysis. Mutations in the gene G6PC3 result in significantly reduced enzyme activity leading to impaired glucose homeostasis and specifically causing increased neutrophil apoptosis and neutropenia. In addition, functional defects are demonstrated: aberrant glycosylation seems to impair oxidative burst in pathogen killing pathway [9,10].

Multiple mutations have been identified, but genotype-phenotype correlations will require further investigations. Severe neutropenia, that is the key marker in all cases, is associated with recurrent and/or severe infections by the first months of age. However, most of the patients develop additional manifestations that are typical of this syndrome [9]. A prominent venous pattern should be looked for in children, while it becomes more evident in the adult age. Congenital heart diseases and uro-genital malformations are characteristic and should be investigated when G6PC3 deficiency is suspected. Atrial septal defects are common, but also valvular anomalies are described. In males, genital anomalies are more frequent, mainly including cryptorchidism, inguinal hernia, vescico-uretric reflux, while ambiguous genitalia, micropenis, and genital dysplasia are rare. Notably, failure

Table 1
Clinical manifestations and laboratory findings suggesting the differential diagnosis.

	WHIM syndrome	G6PC3 deficiency	GATA2 deficiency	STK4 deficiency	Reticular dysgenesis	DNA repair disorders
Recurrent/Severe infections	+	+	+	+	+	+
Verrucosis	±	–	±	±	±	±
Mycobacterium infections	–	–	±	–	±	±
Mucocutaneous candidiasis	–	–	–	±	±	±
Failure to thrive	–	±	–	–	+	+
Congenital heart disease	±	±	–	±	–	–
Uro-genital anomalies	–	±	–	–	–	–
Facial dysmorphism	–	±	±	–	–	+
Sensorineural deafness	–	–	–	–	+	–
Ectatic superficial veins	–	±	–	–	–	–
Lymphedema	–	–	±	–	–	–
Endocrine disorders	–	±	–	–	–	–
Autoimmune disorders	–	–	–	±	–	–
Malignancies	±	–	±	±	–	+
Neutropenia	+	+	+	±	+	+
Lymphopenia	+	±	+	+	+	+
Monocytopenia	+	–	+	–	+	+
Hypogammaglobulinemia	±	–	–	–	+	+
Thrombocytopenia	–	±	–	–	–	–
Myelokathexis	+	±	–	–	–	–
BM hypocellularity	–	±	+	–	+	+