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RESEARCH ARTICLE

CHRONIC NEUTROPENIA REVEALING HYPER IGM SYNDROME: A CASE REPORT

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Abstract

Hyper IgM syndrome is a well-knownhereditaryimmunodeficiency, first describedin 1961. It iscaused by a defect in B lymphocytes, characterized by a normal or high serumlevel of IgM and a low or zerolevel of IgG, IgA, IgE resultingfrom a deficiency in isotype switching. Itsclinical manifestations are dominated by recurrent infections, especiallyrespiratory and digestive. The interest of this article is to illustrate a particular mode of revelation of hyper IgM syndromes through persistent chronicneutropenia in an infant.

Introduction:-

Hyper IgM syndromes (SHIM) or Class Switch RecombinationDeficiencies (CSR-Ds) constitute a heterogeneous and rare group of immunodeficiencies, characterized by the association of a profounddeficiency in IgG, IgA, and a normal or elevatedlevel of Ig M. They are caused by a defect in isotype switching in association or not with a defect in somatichypermutation in B lymphocytes [1]. CSR-Ds are classifiedinto 6 types, depending on the gene and the mutatedprotein: SHIM1 (CD40L), SHIM2 (AID), SHIM3 (CD40), SHIM5 (Ung), SHIM6 (NEMO) and SHIM7 (IKBA) [2]. In addition to recurrent infections which are the mostcommon manifestations in the majority of cases, a number of patients sufferfromneutropenia.

Herewe report the case of a 2-year-old childwithchronic and persistent neutropeniawhosubsequentlyrevealed a hyper-IgM syndrome.

Case report :

This was a 2-year-old boy from a non-consanguineousmarriage, wellvaccinated, with 2 healthysistersaged 10 and 17 respectively, a healthybrotheraged 19, no evidence of death in infancy and no similar cases in the family. Hispersonalhistoryincluded an anal abscess at the age of 15 months. He washospitalized at the age of 18 months for stomatitiswith gingival hypertrophy, the initial assessment of whichrevealedprofound and persistent neutropenia at 556 controlledafter 15 days at 430.

Clinical exam on admission: No dysmorphic syndrome; weight= 13 kg (N), size= 95 cm (+2SD); the stomatologicalexaminationshowedsignificant gingival hypertrophy, hemorrhagic and painfulerosivegingivitisassociatedwithaphthae (figure 1); the pleuropulmonary and cardiovascularexaminationwereunremarkable, no hepatosplenomegaly, no bone or joint pain, the lymphnode areas are free. The rest of the examinationis normal.

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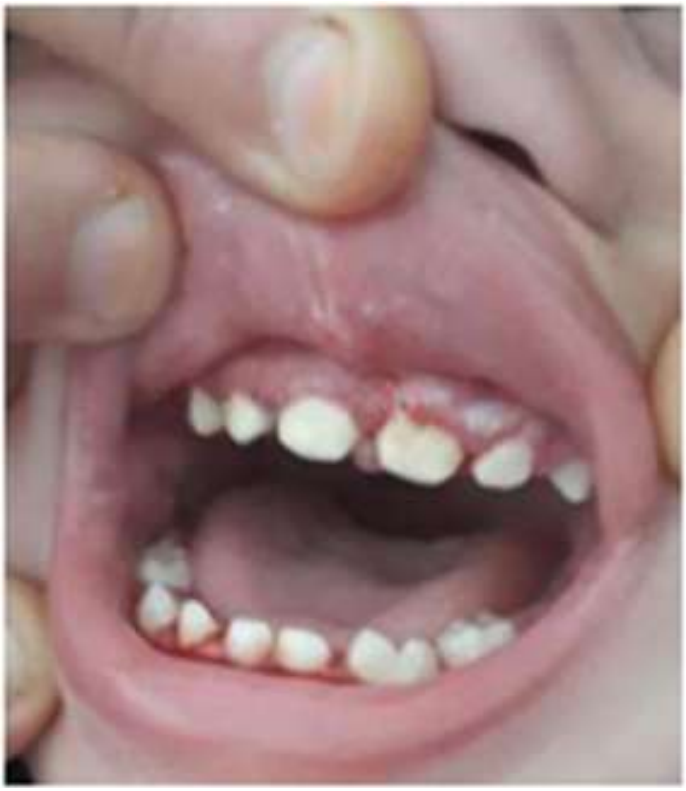
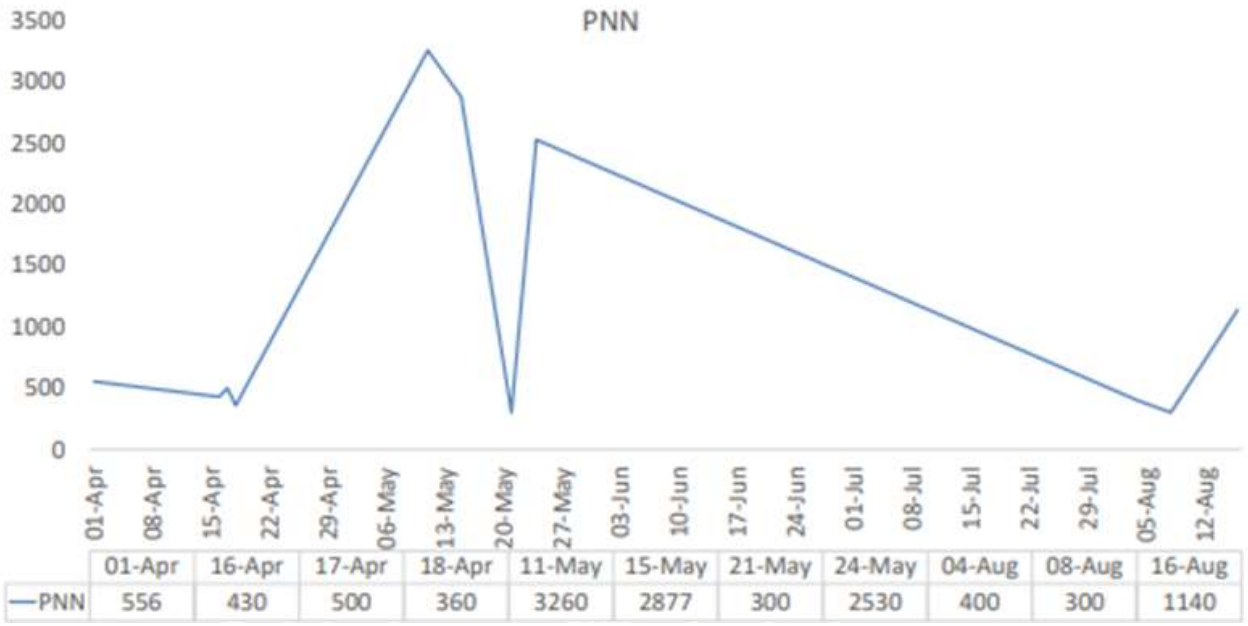


Figure 1:- Gingival hypertrophy, hemorrhagic and painfulerosivegingivitisassociatedwithcanker sores.

An initial assessmentwascarried out: Blood count: GB: 9100 including 500 PNN and 6600 Lymphocytes, Hb = 11.1g / dl, VGM = 69.2fl, TCMH = 23pg, Platelets = 402000. Liver, phosphocalcic, lipid and proteinlevels: normal. Albumin, Vitamin B12 and B9 are normal. Ferritinisalso normal. Radiologicalexaminationsincludingchest X-ray and abdominal ultrasound are withoutparticularities. The serological profile (HVB, CMV, HIV, rubella) wasnegative. A myelogramrevealed the presence of 5% blast cellswith the neutrophilicgranularlineage at 16%.A weight dosage of immunoglobulins and lymphocyte subpopulationswasdoneshowing the resultsillustrated in the following table:

Case	Igweight dosage				lymphocyte subpopulation count				
	IgM(g/l) (0,16-1,32)	IgG(g/l) (4,42-8,95)	IgA(g/l) (0,160-0,980)	IgE(UI/ml) (0,1-200)	lym	CD3+	CD4+	CD8+	CD19+
August 16th	1.38	0.03	0.04		7430	74.6% 5534	66% 4904	7.2% 535	20%
August 26th	1.31	0.02	0.04	< 0,1	8180	71.4% 5841	62.3% 5096	7.6% 622	19%

The dosage of anti-vaccineantibodiesrevealed the absence of anti-diphtheria AC, a control of anti-tetanusimmunitylessthan 0.03 and of immunityagainst H. influenzae type b lessthan 0.1. A control of the PNN rate wascarried out on this patient on a weeklythenmonthly basis showing the results (figure 2):



	01-Apr	16-Apr	17-Apr	18-Apr	11-May	15-May	21-May	24-May	04-Aug	08-Aug	16-Aug
PNN	556	430	500	360	3260	2877	300	2530	400	300	1140

Figure 2:- Curveshowing the evolution of the PNN rate as a function of time.

The mostlikelydiagnosis in our patient ishyperimmunoglobulin M syndrome, probably type 3. The patient was put on monthly infusion of polyvalent immunoglobulins and treatmentwith cotrimoxazole, G CSF if severeneutropenia.

Discussion:-

Hyper-IgM syndromes are very rare immunodeficiencies, first describedin 1961 by Rosen et al [3]. In Morocco, theyrepresent 2.8% of primaryimmunodeficiencies.

The causes are molecular and can classify HIGM syndromes which are linkedeither to a signalingdefectbetween T and B lymphocytes, or to intracellular signal transmission defectsinduced by the interaction between CD40L and CD40. X-linked hyper IgM syndrome wouldrepresent the mostfrequent hyper-IgM syndromes [4] especially "in Europe where the consanguinity rate isverylow. The American registry reports that the minimum incidence rate of X-HIGM wasapproximately 1 case per 1,030,000 live births [5]. AID deficiencyisranked 2nd in frequencyafter X-HIGM. Minegishisuggestedthat 50% of non-X-linked hyper IgM syndromes were HIGM2 syndromes [6]. The otherforms, autosomal recessive or dominant, are clinicallyheterogeneous. Several types are individualizedaccording to the mutatedgene and protein: the mostfrequent are SHIM1 (CD40L), SHIM2 (AID), SHIM3 (CD40), SHIM5 (UNG), SHIM6 (NEMO) and SHIM7 (IKBA).

Clinical manifestations developduring the first or second year of life for the majority of patients and are dominatedmainly by: Recurrent infections (pulmonary, ENT, digestive), Opportunistic infections, Signs of autoimmunity and Lymphoproliferation[7]. The weight dosage of immunoglobulinsis the essential element for diagnosiswith a normal or increasedlevel of IgM and a low or zerolevel of IgA, IgG, IgE. The count of lymphocyte subpopulationsis normal, we note decrease or absence of the expression of CD40 and reduction or absence of the expression of CD40L. The geneticstudyconfirms the diagnosis and specifies the type of HIGM [8].For our patient, SHIM type 3 is the mostlikelydiagnosisgiven: earlyage, healthybrother, neutropenia, recurrent infections and the absence of hypertrophy of lymphoidorgans.

Ig replacement therapyis essential to correct the clinicalconsequences of the humoral deficiencypresent in all forms of HIGM syndrome. In HIGM 2, HIGM 4 and HIGM 5 syndromes, treatmentisbasedmainly on IV Ig, whichsignificantlyreduces the incidence of bacterial infections. In HIGM1 and HIGM3 syndromes, treatmentwith IV Ig and TSU-basedantibioticprophylaxisisindicated in the majority of patients awaiting HSCT, thusreducing the frequency and severity of infections but does not preventlymphoproliferativedisease, sclerosingcholangitis and malignantdiseases [9].

Conclusion:-

NeutropeniaissometimesassociatedwithhyperIgM syndrome, but the reasonisunclear. Prophylactictreatmentwith cotrimoxazole and intravenous gamma globulin prevents infections and mayalleviateneutropenia.

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