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Alloimmune thrombocytopenia associated with neutropenia in a 8-week old boy – a case report**

Alloimmunologiczna małopłytkowość z towarzyszącą neutropenią u 8-tygodniowego chłopca – opis przypadku

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Słowa kluczowe

alloimmunologiczna cytopenia, małopłytkowość, neutropenia, przeciwciała przeciwleukocytarne, przeciwciała przeciwpłytkowe

Summary

The most common cause of thrombocytopenia in infants in the first months of life are infections, while destruction of platelets in the course of immunological reactions occurs less frequently. In the case of the alloimmune reactions symptoms may appear as early as in the fetal life or shortly after birth and are caused by maternal antibodies passing through the placenta. The antibodies are most often directed against platelet antigens (anti-human platelet antigens – anti-HPA) of the child, inherited from the father. Much less likely to cause thrombocytopenia are leukocyte antibodies (anti-human leukocyte antigens – anti--HLA). They are, however, detected in 7-39% of pregnant women in serum, but they rarely cause neonatal alloimmune cytopenias. A few cases of thrombocytopenia in neonates of mothers with anti-HLA antibodies, but not anti-HPA, present in serum have been described in the literature. However, there are occasional reports of simultaneous thrombocytopenia and neutropenia in these children.

The paper presents a case of a boy in whom severe thrombocytopenia and neutropenia occurred in the 8th week of postnatal life. The patient was treated with infusion of immunoglobulins with a good effect. The hematologic abnormalities resolved completely after 3 months of age. Taking into account the course of the disease and the exclusion of other reasons of cytopenia, alloimmune thrombocytopenia and neutropenia was suspected. There was no incompatibility in platelet antigens of the parents. However, anti-HLA were detected in maternal serum, which most probably was the reason of the thrombocytopenia and neutropenia in the child.

Streszczenie

Najczęstszą przyczyną małopłytkowości u niemowląt w pierwszych miesiącach życia są infekcje, rzadziej niszczenie płytek w przebiegu reakcji immunologicznych. W przypadku reakcji alloimmunologicznych objawy mogą pojawić się już u płodu bądź wkrótce po urodzeniu i są spowodowane przechodzącymi przez łożysko przeciwciałami matczynymi. Przeciwciała te najczęściej są skierowane przeciwko antygenom płytkowym (ang. *anti-human platelet antigens* – anty-HPA) dziecka, odziedziczonym po ojcu. Znacznie rzadziej przyczyną małopłytkowości są przeciwciała przeciwleukocytane (ang. *anti-human leukocyte antigens* – anty-HLA). Można je wykryć w surowicy krwi u 7-39% ciężarnych, ale rzadko wywołują noworodkowe alloimmunologiczne cytopenie. W literaturze opisano przypadki małopłytkowości u noworodków, u matek których wykryto w surowicy jedynie przeciwciała anty-HLA, bez obecności anty-HPA. Jednakże sporadyczne są doniesienia o równoczesnej trombocytopenii i neutropenii u tych dzieci.

Konflikt interesów
Conflict of interest

Brak konfliktu interesów
None

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W pracy przedstawiamy przypadek chłopca, u którego ciężka małopłytkowość i neutropenia pojawiły się w 8. tygodniu życia. W leczeniu zastosowano wlew immunoglobulin z dobrym efektem. Zaburzenia hematologiczne ustąpiły całkowicie po 3. miesiącu życia. Na podstawie przebiegu choroby i po wykluczeniu innych przyczyn wysunięto podejrzenie alloimmunologicznej cytopenii. Nie stwierdzono niezgodności antygenów płytek krwi rodziców. W surowicy krwi matki były natomiast obecne przeciwciała antyleukocytarne (anty-HLA), które zapewne były przyczyną choroby.

INTRODUCTION

Thrombocytopenia in infants, defined as a platelet count below 150 000/μl, requires a rapid diagnosis and a targeted treatment. The greatest danger is a bleeding into the central nervous system, which may be fatal (1). The differential diagnosis includes two main reasons for thrombocytopenia, which are a condition associated with: (A) insufficient platelet production and (B) an excessive destruction or loss of platelets. Two or, less often, more causes of thrombocytopenia may potentially co-exist in a particular patient (2).

A. An insufficient production of platelets may be caused by various factors. In infants, the most common cause is an ongoing infection. Other causes of thrombocytopenia include nutritional deficiencies, bone marrow failure (as a result of aplastic anemia, myelodysplastic syndromes or drug toxicity), tumor cell infiltrates that dominate over megakariocytosis in bone marrow. Thrombocytopenia is also one of the symptoms of genetic syndromes, e.g. the Fanconi syndrome, Wiskott-Aldrich syndrome, Thrombocytopenia-absent radius syndrome (TAR syndrome).

B. Excessive destruction of platelets leading to thrombocytopenia may have two main causes: non-immunological and, on the other hand, antibody-induced. The destruction of platelets that is independent of immune mechanisms is characteristic for disseminated intravascular coagulation (DIC), the hemolytic uremic syndrome, heart defects, hypersplenism, large hemangiomas and other conditions (2).

The most frequent cause of thrombocytopenia in children is platelet consumption in the course of immune reactions caused by auto- or alloantibodies directed against platelet antigens. Autoantibodies lead to the destruction of platelets in the course of the immune thrombocytopenia (ITP) and autoimmune diseases (e.g. lupus erythematosus). Thrombocytopenia may also be drug-induced. Alloantibodies, which are antibodies derived from another person, initiate the destruction of the donor platelets after blood transfusions. The particular case when alloantibodies may possibly be present in the child's serum is pregnancy, when maternal antibodies get into the bloodstream of the fetus through the placenta.

Neonatal alloimmune thrombocytopenia (NAIT) is caused by maternal IgG antibodies directed against platelet antigens of the child, inherited from his father. The pathomechanism of NAIT is analogous to the hemolytic disease of the newborn caused by the Rh incompatibility. In contrast to that condition, the symptoms of NAIT may appear in the fetus or neonate already in the first pregnancy, however, in the following child they are much more severe (3). What is more, in NAIT the serum antibodies titers are not associated with the incidence or severity of the thrombocytopenia (4). The child may present varying degrees of disease severity, from a mild thrombocytopenia to a severe one, leading to spontaneous intracranial bleeding, which may affect up to 25% of the infants (1, 5). The symptoms disappear within a few weeks. In principle, the mother presents no abnormalities. An accurate diagnosis of a possible platelet incompatibility in the child is essential for the safety of the parents' next child.

The criteria for the diagnosis of neonatal alloimmune thrombocytopenia include a statement of thrombocytopenia in the newborn or fetus, identification of a platelet antigen in the father, fetus or the newborn not found in the mother, and detection of maternal antibodies against that antigen (tab. 1) (5).

The most common platelet incompatibility in Caucasians is caused by the HPA-1a (6), followed by the HPA-5b and the HPA-15 (5, 7). Alloimmunity in the HPA-1a induces the most severe symptoms (8). Individual cases of neonatal alloimmune thrombocytopenia were associated with the presence of alloantibodies directed against human leukocyte antigens (anti-human leukocyte antigens – anti-HLA) (9, 10). These antigens are in fact also present in platelet cell membranes (11). Hardly ever was the presence of anti-HLA antibodies in the mother associated with the occurrence of neonatal thrombocytopenia and neutropenia at the same time (7, 12-14). In the study we present a case of a 8-week old boy with thrombocytopenia co-occurring with neutropenia, caused by gamma globulins present in his mother's serum that were directed against the HLA class I antigens.

Tab. 1. Criteria for neonatal alloimmune thrombocytopenia diagnosis. Data from (8)

Criteria for the diagnosis of neonatal alloimmune thrombocytopenia
– fetal or neonatal thrombocytopenia – identification of a parental, fetal or neonatal platelet antigen that the mother lacks – identification of maternal antibodies to that antygen

CASE DESCRIPTION

An 8-week old boy was sent to hospital because of numerous petechiae and bruises, which, according to

the mother, appeared due to child's restlessness and crying caused by a stomachache. Single skin lesions similar to petechiae were possibly observed by her since his birth, but she linked it with food allergy. The mother did not notice any signs of infection, including fever. Two weeks before admission he was vaccinated with DTaP + Hib and against hepatitis B, without any complications. Until admission he had only received prophylactic doses of vitamins K and D.

The boy was born from the first pregnancy; the childbirth took place vaginally at 41 weeks, with a body weight of 3710 g, length of 55 cm, 10 points of the Apgar scale. The parents were young and healthy. No autoimmune diseases were diagnosed in the mother and all the complete blood counts performed during pregnancy were normal. Assays for the cytomegalovirus (CMV IgG positive, IgM negative), rubella (IgG positive, IgM negative) and toxoplasmosis (IgG and IgM negative) did not confirm acute infections with these pathogens during pregnancy. Further assays also excluded human immunodeficiency virus (HIV), syphilis, hepatitis type C (HCV) and group B streptococci (GBS, *Streptococcus agalactiae*) infections. The prenatal ultrasound examinations were normal and showed no signs of possible bleeding. The neonatal period of the boy was uneventful. The child was breastfed on demand, normal weight gain was observed. There was neither bleeding from the umbilical cord stump nor bruises after intramuscular administration of vitamin K or after vaccinations. No blood counts were performed in the child until the admission.

On admission to our ward, the boy was in a relatively good general condition, but anxious. In the physical examination jaundice was not noticed, but the skin was covered by many petechiae and small bruises on the face, especially around the eyes, on the neck, the trunk and on the limbs (fig. 1 and 2). The petechiae and ecchymoses were found on the soft palate. The left axillary lymph node was 1-1.5 cm in diameter, shifting, seemed painful; the skin over it was unchanged. The other peripheral lymph nodes were not detected. The abdomen was soft, painless, the liver palpable to 2.5 cm, the spleen palpable to 0.5 cm below the costal margins. No other abnormalities were found in the physical examination. Laboratory tests at admission indicated low markers of inflammation, i.e. acute phase protein (C-reactive protein – CRP) – 0.35 mg/L and procalcitonin (PCT) – 0.08 ng/μl. The red and white blood cell counts were appropriate to the patient's age (Hb – 11.5 g%, RBC – 3.7 million/μl, MCV – 90 fl, WBC – 11 000/μl, granulocytes – 2310/μl and lymphocytes – 7230/μl). Only the number of platelets was significantly reduced to 5000/μl. The biochemical assays: electrolytes, renal and liver function parameters, coagulation – were correct. The urinalysis was without any deviation. Table 2 presents the results of the complete blood counts of the boy performed during hospitalization and the subsequent visits at the hematology ambulatory care.

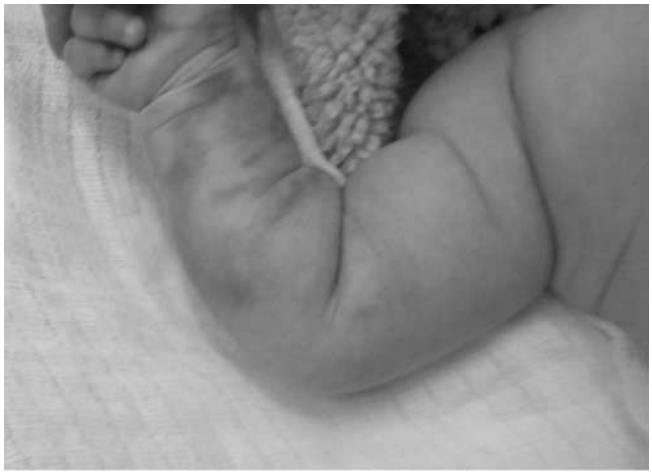

Fig. 1. Massive petechiae and bruises on the boy's arm

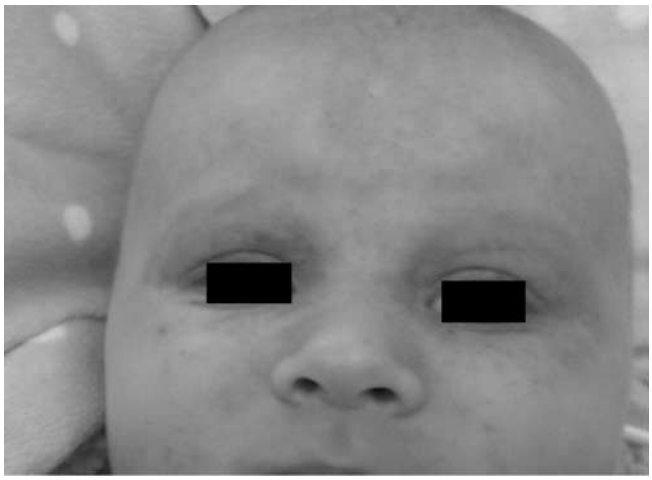

Fig. 2. Massive petechiae and bruises on the boy's face, especially around the eyes

Based on the history, the physical examination and the results of the additional assays, thrombocytopenia was diagnosed. Taking into account the fact that the cause of the disease was immunological, the patient received human immunoglobulin intravenously (IVIG). A dose of 5 g IVIG in total, i.e. 0.8 g/kg body weight, was administered.

The boy remained in a relatively good general condition during the first two days of the hospital stay. The vital parameters were normal. No fever and other signs of infection were noticed. Slight graying of the skin around the mouth was observed while the child was crying. The blood analysis performed on the second day of his stay indicated low markers of inflammation again. The platelet count increased to 27 000/μl, but there was observed a decrease in the white blood cell number to 4800/μl with a neutropenia – 480 cells/μl (the normal range for the age is: 6000-14 000/μl WBC, granulocytes above 1000 cells per μl) and a normocytic anemia (Hb 9.8 g%, MCV 91 fl) (the standard for the age is respectively: Hb 11.1 ± 1.1, MCV

Tab. 2. The results of complete blood counts of the boy obtained during hospital stay and ambulatory hematological care. The age of the boy, day of the hospital stay and doses of intravenous immunoglobulins (IVIG) are provided

Complete blood count parameters	Data obtained during hospitalization (day of the hospital stay)				Data from Hematological Ambulatory Care			
Age of the boy	8 wk (0)	8 wk (1) after 1. dose of IVIG	8 wk (2) after 2. dose of IVIG	8 wk (4)	2.5/12	3/12	5/12	15/12
RBC (x $10^9/\mu l$)	3.7	3.2	3.1	3.0	3.6	4.3	5.1	5.07
Hb (g/dl)	11.5	9.8	9.7	9.4	10.7	11.9	12.3	12.9
MCV (fl)	90	91	90	91	89	83	75	80
WBC (x $10^3/\mu l$)	11.7	4.8	6.3	4.5	5.7	6.7	5.8	5.3
Neutrophils (x $10^3/\mu l$)	2.31	0.48	0.61	0.58	0.37	0.94	1.16	1.70
Neutrophils (%)	19.8	10	9.7	12.8	6.5	14	20	33
Lymphocytes (%)	61.8	66.6	66.8	59.9	77.5	69	75	59
Platelets (x $10^3/\mu l$)	5	27	119	263	668	512	381	213

100 ± 13.0 fl) (15). The peripheral blood smear was normal. The ultrasound of the abdomen and the central nervous system as well as the radiographic chest examination showed no abnormalities. The electrocardiogram was normal. In the echocardiography a bicuspid aortic valve was found for further observation. Due to the low platelet count, an infusion of immunoglobulin (IVIG) (again at the dose of 0.8/kg) was repeated after 24 hours. As a result, the platelet count rose to 119 000/μl. From the third day on, the child's condition improved, the skin lesions gradually disappeared, a weight gain was observed. Probiotic supplementation and hematopoietic vitamin were administered. A delayed administration of oral iron was recommended, due to slightly diarrheal stools (with no blood trace). On the 4th day of the hospital stay, the platelet count was already normal (263 000/μl); the anemia and neutropenia remained. The boy was discharged from the ward with a recommendation for further care in an outpatient hematology clinic for children.

The control platelet counts after discharge were normal. The neutropenia persisted for a longer period: at 5 months age the granulocyte count was 1160/μl; in the 15th month of life it was already normal (over 1500/μl). Iron and hematopoietic vitamins were administered due to the anemia and iron deficiency.

Both parents were found to be homozygotes in terms of the HPA-1a antigen gene. Therefore, an incompatibility in HPA-1 was excluded. Anti-HLA IgG were detected in the maternal serum. It was recommended to assess the antiplatelet antibodies about the 15th week of a subsequent pregnancy of the mother.

DISCUSSION

Based on the history, physical examination, and the response to treatment, it was found that the most probable cause of the clinical condition in the 8-week old boy was alloimmune thrombocytopenia. Most likely, the ecchymosis were appearing on the boy's skin from birth on, which was neglected by his parents. This may be the first evidence to support this diagnosis. Unfortunately, no complete blood counts were performed in the boy after birth, and therefore the platelet count was not known at that time. In addition, the good clinical condition of the boy, despite the severe symptoms, as well as the rapid response to treatment with immunoglobulins also indicates the immunological cause of the disease. An indirect confirmation of the diagnosis was the detection of antileukocyte antibodies (anti-HLA) in the maternal serum, which were probably the cause of the child's illness. Other known causes of thrombocytopenia, such as: viral infection (including cytomegalovirus), generalized infection, coagulation disorders including disseminated intravascular coagulation syndrome, tumor growth or artifacts, were excluded through the differential diagnosis carried out after hospital admission.

Two facts that were unusual for a typical course of alloantibodies-induced thrombocytopenia were found in the boy's case. The first one was that the severe symptoms of the disease did not occur in him until the 8th week of age. Furthermore, it is impossible to indicate the factor that triggered such a strong immune response. Alloimmune thrombocytopenia usually occurs in the neonatal or even the prenatal period. The symptoms disappear within a few weeks (5). On the other hand, infections and vaccinations are the leading trigger for such immune reactions. The blood assays performed in the patient permit us to exclude an ongoing infection. Although the boy was vaccinated (with Infanrix and Hepavax) two weeks before the onset of the symptoms, the use of the "killed" vaccines is not associated with occurrence of thrombocytopenia (16, 17). This might be a side effect, but it is rather characteristic for vaccines that contain "live" viruses, es-

pecially vaccinations against measles, mumps and rubella (18).

Usually, the cause of alloimmune thrombocytopenia in neonates is the presence of maternal antibodies directed against platelet antigens (HPA) of the child that were inherited from the child's father. In the parents of the child, however, there was no incompatibility of platelet antigen as far as the antigen most common in Caucasians, i.e. the HPA-1a, is taken into account. The incompatibility with regard to that antigen is associated with the most severe thrombocytopenia course (8). Almost 25% of the affected fetuses or newborns may have intracranial bleeding, the consequence of which is delayed psychomotor development or even death (1). In the case presented here, both the mother and the father of the child were found to be homozygous for the HPA-1a. No other platelet antigens were tested against which immunization of the mother and the transfer of antibodies through the placenta may have taken place. In the literature, other antigens may induce alloimmune thrombocytopenia less infrequently and with a degree of severity lower than in the case of the HPA-1a. These antigens are the HPA-5b, HPA-1b and HPA-15. The prevalence of these antigens on the platelet surface is low (approximately 2%) in our population, therefore, there is an insignificant likelihood that the child would inherit other antigens than the maternal ones and that the incompatibility would be clinically relevant (19).

Not only anti-platelet antibodies, but also the antibodies directed against the leukocyte antigens (HLA) present in maternal serum may induce alloimmune cytopenia in a child. There are case reports that confirm the relationship of thrombocytopenia in fetuses or newborns and the presence of anti-HLA in the mother (12, 13). This is possible because the HLA antigens, found typically on leukocytes, are also present in large quantities in the platelet cell membranes. About 5% of women who produce this type of antibodies during pregnancy also produce antibodies which are directed against the antigens present on the fetal blood platelets (20). The frequency of this type of immunization during pregnancy is relatively high, because it affects as many as 7-39% of pregnant women (13). According to literature data, the expression of the HLA antigens on the granulocytes in neonates is relatively weak, and therefore, the incidence of neutropenia in the conflict HLA, compared with thrombocytopenia, is significantly lower (21). If neutropenia occurs, it is usually, as in the case described here, accompanied by thrombocytopenia. Isolated alloimmune neutropenia in newborns is usually caused by antibodies directed against human neutrophil antigens (HNA).

Alloimmune cytopenias may occur due to incompatibilities in several antigens found on different cell types at the same time (7, 12, 14). Taaning et al. (7) present a case of neonatal thrombocytopenia and neutropenia caused by a simultaneous incompatibility in the neutrophil (anti-HNA-1b) and platelet (anti HPA-3a) antigens. The resolution of the disease was achieved only thanks to the transfusion of a platelet concentrate with a specific phenotype, i.e. without HPA-3. Marin et al. (12) reported a case of a co-existence of neutropenia and thrombocytopenia in a neonate caused by the concurrent presence of 3 types of antibodies – anti-platelet (anti-HPA-3b), anti-neutrophil (anti-HNA-1a) and anti-leukocyte (anti-HLA). The patient initially received immunoglobulin infusion, however, with no desired effect. The normalization of the neutrophils was reached only after the administration of the granulocyte colony stimulating factor (G-CSF).

In the case described here, an immunoglobulin infusion caused a rapid improvement in the platelet counts. After 2 doses of the IVIG, the platelets rose from 5000/μl to 119 000/μl. The neutropenia, which appeared shortly after the first IVIG infusion, subsided after 3 months of age, which is when the antibodies derived from the mother through the placenta dissapear. In contrast to the course of the disease described by Marin et al. (12), our patient did not require additional treatment, because the neutrophil count was 480 cells per μl and there was no infection. The concomitant anemia associated with the frequent retrievals of blood in the child was treated with iron and hematopoietic vitamins with a good effect. A definite exclusion of the immunological destruction of erythrocytes by the anti-HLA antigens is not possible, but rather unlikely, because the expression of the HLA on the erythrocyte membranes is very slight (22). There was no recurrence of abnormalities in the blood counts over the subsequent observation of the boy, which lasted up to 15 months of age in an outpatient hematology clinic.

The occurrence of an alloimmune thrombocytopenia in a child is a risk factor of hematological abnormalities during the subsequent pregnancy of the parents and in the offspring of the sister of the child's mother (8). Unfortunately, there is no parameter known that might anticipate the occurrence or the severity of such possible alloimmune reaction. In order to ensure the safety of the parents' next child, a diagnostic algorithm of alloimmune thrombocytopenia is proposed (fig. 3). It applies to the siblings of children who were diagnosed with thrombocytopenia or with intracranial bleeding of an unknown cause. The algorithm takes into account performing blood counts in the mother, examining the platelet antigens in both parents, assessing the antiplatelet antibody production in the mother and performing a direct analysis of the maternal serum reaction to the father's platelets in the particular weeks of pregnancy. In the case of an alloimmune thrombocytopenia diagnosed during pregnancy, the currently proposed treatment in the mother is based on immunoglobulins administered weekly, the use of corticosteroids or performing a transfusion of a platelet concentrate with a specific phenotype to the fetus (5).

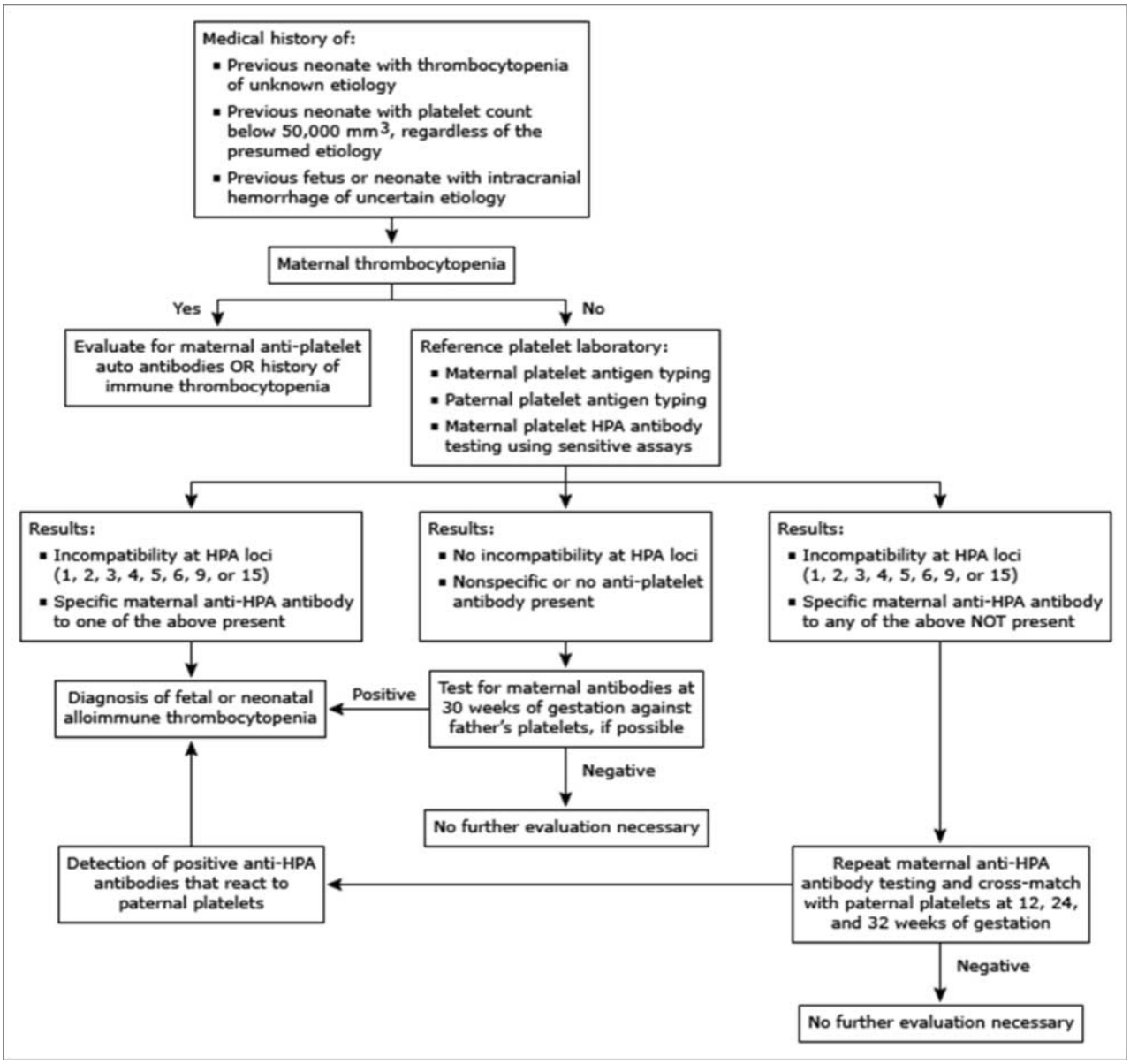

Fig. 3. Algorithm of neonatal alloimmune thrombocytopenia. Data from (8)
HPA – human platelet antigens

CONCLUSIONS

Alloimmune thrombocytopenia and neutropenia was diagnosed in the case described, after other causes of cytopenia had been excluded. The symptoms appeared in the boy at an unusual time, that is, in his 8th week of life, without an apparent reason. The patient was treated with intravenous immunoglobulins with a good effect. The hematologic abnormalities resolved completely after 3 months of age. There was no incompatibility in the platelet antigens (HPA) of the mother and the father. In contrast, antileukocyte antibodies (anti-HLA) were detected in the maternal serum, which were the most likely cause of the boy's disease. An analysis of the disease causes and the data derived from the parents' examinations are very important for the safety of their following child.

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