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Original Article
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Clinical, histopathological, and hematological changes due to isoimmune thrombocytopenic purpura in piglets[1]

Jean Carlo O. Menegatt[2], Amauri Rigo[3], Maurício Mezaroba[4], Adriano Tony Ramos[5], Conrado O. Gamba[6], Carolina Reck[6] and Álvaro Menin[5]*

ABSTRACT.- Menegatt J.C.O., Rigo A., Mezaroba M., Ramos A.T., Gamba C.O., Reck C. & Menin A. 2023. **Clinical, histopathological, and hematological changes due to isoimmune thrombocytopenic purpura in piglets.** *Pesquisa Veterinária Brasileira 43:e07071, 2023*. Departamento de Biociências e Saúde Única, Universidade Federal de Santa Catarina, Rodovia Ulysses Gaboardi Km 3, Curitibanos, SC 89520-000, Brazil. E-mail: alvaro.menin@ufsc.br

Isoimmune thrombocytopenic purpura (ITP) is an immune-mediated disease that causes severe hemorrhagic lesions and high mortality in piglets. The disease can occur early in newborn piglets (EITP) or late in 2- to 3-week old piglets (LITP). In this study, we analysed the clinical, pathological, and hematological aspects of 391 ITP cases (312 with EITP and 79 with LITP). In LIPT cases, morbidity and mortality rates were higher, with rates of 60% (morbidity) and 53% (mortality). The main clinicopathological findings in ITP cases were different patterns of hemorrhages organs and tissues. In EITP, clinical signs were characterized by extensive subcutaneous hemorrhages and death occurred within a few days; however, in LITP, often sudden death occurred. In macroscopic analysis, hemorrhagic diathesis was observed in all affected animals. In EITP, the most severe hemorrhagic lesions were integumentary, mainly in the dermis and epidermis. In LITP, visceral lesions were predominant, mainly in the epicardium and intestines. Microscopic bone marrow analysis revealed mild cellular hyperplasia in EITP and bone marrow aplasia in LITP. hematological analyses revealed leucopenia, thrombocytopenia, and anemia in all ITP-affected animals. However, fostering by a different sow was only efficient in controlling EITP and had little effect in LITP-symptomatic piglets, due to more severe lesions. Further studies on the etiopathogenesis of LITP are required to improve our understanding of this disease form.

INDEX TERMS: Veterinary diagnosis, immunopathology, management, animal health, thrombocytopenia, piglets, pigs.

RESUMO.- [**Alterações clínicas, histopatológicas e hematológicas decorrentes de púrpura trombocitopenica isoimune em leitões.**] Púrpura trombocitopênica isoimune (PTI) é uma doença imunomediada que causa lesões hemorrágicas graves e alta mortalidade em leitões, que pode se apresentar através de uma forma precoce em leitões neonatos (PTIP) ou uma forma tardia em leitões com duas a três semanas de idade (PTIT). Neste trabalho analisamos aspectos clínicos, hematológicos e histopatológicos de 391 casos de PTI, sendo 312 de PTIP e 79 de PTIT. Observou-se maiores morbidade (60%) e mortalidade (53%) na PTIT. Os principais achados clínico-patológicos observado na PTI são hemorragias em diferentes graus de intensidade e nos diferentes órgãos e tecidos. Na PTIP observou-se predominantemente hemorragias subcutâneas extensas e morte em alguns dias, já na PTIT, observou-se além de grave hemorragia, morte súbita. Na análise macroscópica, observou-se diátese hemorrágica em todos os animais afetados. Na PTIP as lesões hemorrágicas mais graves foram tegumentares, principalmente em derme e epiderme, enquanto, na forma tardia, observou-se lesões

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[2] Setor de Patologia Veterinária, Faculdade de Veterinária, Universidade Federal do Rio Grande do Sul, Av. Bento Gonçalves 9090, Porto Alegre, RS, 91540-000, Brasil.

[3] Pamplona Alimentos S/A, Departamento de Fomento, Rio do Sul, SC, Brasil.

[4] Laboratório Veterinário Amigo Vida, Videira, SC, 89560-380, Brasil.

[5] Departamento de Biociências e Saúde Única, Universidade Federal de Santa Catarina, Rodovia Ulysses Gaboardi, Km 3, Curitibanos, SC, 89520-000, Brasil. *Corresponding author: alvaro.menin@ufsc.br

[6] VERTA Laboratórios, Instituto de Pesquisa e diagnóstico veterinário, Avenida Lions, 1380, Curitibanos, SC, 89520-000, Brasil.

predominantemente viscerais, em epicárdico e intestino. A análise microscópica de medula óssea revelou discreta hiperplasia celular na forma PTIP, enquanto, na PTIT observou-se aplasia medular. Na análise hematológica observou-se leucopenia, trombocitopenia e anemia em todos os animais com PTI. Os achados clínicos, histopatológicos e hematológicos para PTIP e PTIT da doença permitiram o diagnóstico de PTI. Entretanto, a troca de mãe se mostrou eficiente apenas para controle PTIP, uma vez que, esta estratégia apresenta pouco resultado para leitões sintomáticos com a PTIT, devido lesões mais severas. Estudos sobre a etiopatogênese da PTIT ainda são necessários para melhor entendimento desta forma da doença.

TERMOS DE INDEXAÇÃO: Diagnóstico veterinário, imunopatologia, manejo, saúde animal, trombocitopenia, leitões, porcos.

INTRODUCTION

Isoimmune thrombocytopenic purpura (ITP) is an immune-mediated disease, which affects suckling piglets (Dimmock et al. 1982, Kaplan 2006). It is caused by the incompatibility of thrombocyte of the piglets and maternal antibody (Hsu et al. 2016). The sow produces antibodies against the thrombocyte antigens of the boar, which are present in the blood of the piglets (Stormorken et al. 1963, Nordstoga 1965, Dimmock et al. 1982). After ingestion of colostrum with isoimmune antibodies, piglets develop severe thrombocytopenia, and consequently, massive hemorrhages (Galea et al. 1981, Furukawa et al. 2014, Valli et al. 2015, Joller et al. 2020) because isoimmune antibodies cause platelet agglutination and lysis of medullary precursors (megakaryocytes) in newborn piglets (Stormorken et al. 1963, Nordstoga 1965, Saunders & Kinch 1968, Dimmock et al. 1982), leading to clinical signs such as pallor, apathy, multifocal hemorrhaging, and death (Putsche & Kohn 2008). Separating piglets from their mother prior to colostrum consumption and being fostered by a different sow constitutes the main strategy for early treatment of the disease (Schmidt et al. 1977). However, a late form of the disease, also referred to as biphasic thrombocytopenia, can occur in 14-15-day-old piglets. This form is more common and more severe than the early form because platelet destruction and medullary megakaryocytic deficiency lead to a generally fatal thrombocytopenia (Saunders & Kinch 1968, Dimmock et al. 1982).

Animals with ITP show disseminated subcutaneous hemorrhages, severe thrombocytopenia, and anemia, which may affect some or all of the litter (Stormorken et al. 1963, Nordstoga 1965, Saunders & Kinch 1968, Dimmock et al. 1982). Platelet agglutination tests and indirect antiglobulin consumption tests can help diagnose ITP (Kaplan 2006, Hsu et al. 2016); however, typical clinical, hematological, macroscopic, and microscopic findings constitute the main diagnosis strategy (Forster 2007). Because ITP exhibits characteristics of other diseases, the differential diagnosis should include African swine fever (ASV), porcine reproductive and respiratory syndrome (PRRS), warfarin poisoning (Hsu et al. 2016), and systemic inflammatory response syndrome (SIRS).

In Brazil, ITP has been reported more frequently in swine farms that rear pure breeds, which are mainly produced by grandparents and great-grandparents breeding systems. Artificial insemination is a strategy for reducing the likelihood of ITP occurrence (Joller et al. 2020); However, ITP is an emerging disease on commercial swine farms, and recurrent diagnoses occur in different producing regions of world causing mortality from piglets. In this context, the diagnosis of ITP must be rapid and accurate. The aim of this study was to describe a systematic analysis of clinical, pathological, and hematological aspects of early and late ITP on Brazilian swine-breeding farms.

MATERIALS AND METHODS

Animals and clinicopathological examination. The study obtained ethical clearance from the "Universidade Federal de Santa Catarina" (UFSC) ethical review committee (P#5370220221).

In total, 50 litters in which at least one piglet exhibited clinical signs of ITP were systematically examined on two commercial farms. All sows were of commercial crossbreeding, multiparous (two or more parturitions) with no history of litters with ITP. The farms were certified free from ASV, PRRS, and classical swine fever virus (CSFV).

Hematological examination. Blood samples were collected with and without anticoagulant (EDTA) for hematological analyses. Parameters such as the hematocrit, mean corpuscular volume, hemoglobin concentration, mean corpuscular hemoglobin concentration, and platelet count were evaluated. The analysis were performed using an automated veterinary hematology equipment (SDH-3-VET - Labtest®), adjusted for swine, with two-level quality control, and evaluation of Westgard rules by Levey-Jennigs graph. Total platelet and leukocyte values were verified by direct counting in blood smear

Histopathological analysis. All animals that died of ITP (n=174) were analyzed macroscopically and microscopically. Tissue samples (heart, lung, liver, spleen, intestine, mesentery, kidney, bladder, adrenal, muscle, and bone marrow) were fixed in 10% neutral buffered formalin and dehydrated in graded ethanol solutions. Bone tissue was previously decalcified in a formic acid solution. After dehydration, the samples were embedded in paraffin, sectioned (4μm), and stained using hematoxylin and eosin (HE). In bone marrow samples, the presence of megakaryocytes was evaluated, by examination of 10 fields under x400 magnification to determine the degree of injury.

Data analyses. Descriptive analyses of hematology and clinical chemistry parameters were performed using GraphPad Prism 5 (GraphPad Software Inc., San Diego/CA, USA). Results are shown as means and standard deviations.

RESULTS

The 50 affected litters included a total of 648 piglets (520 neonates of 1-3 days old and 128 piglets of 12-16 days old). Of these, 391 piglets were clinically diagnosed with ITP; 80% (312/391) presented with early ITP (EITP) at 1-3 days of age, and 20% (79/391) presented with late ITP (LITP) at 12-16 days of age. The overall rates on farms for EITP was 0.9% and for LITP 1.6%.

LITP symptoms were more severe, with higher rates of morbidity (62%, 79/128), mortality (53%, 68/128), and lethality (87%, 68/79); 30% (24/79) (Fig.1) of piglets with LITP suffered sudden death, whereas 56% (44/79) exhibited a progressive condition including cutaneous hematomas, facial oedema, hyphema, pallor, emaciation, dyspnea, and death within 4-8 days of the onset of clinical signs. Only 14% (11/79) of the animals survived after treatment.

Piglets with EITP showed clinical signs soon after colostrum ingestion. The main changes included cutaneous hemorrhages

in the abdominal region and on the ears and back (Fig.2); 34% (104/312) of the piglets died within 3-6 days of the onset of clinical signs. 66% (208/312) of the animals survived after treatment.

In EITP-affected animals that died (104/312), the pathological analysis indicated the presence of hemorrhagic lesions in the inguinal, axillary, and submandibular lymph nodes in all animals (100%), in addition to lesions on the myocardium (60%, 63/104), serosa of small and large intestines, urinary bladder, and stomach (20%, 21/104). The macroscopic appearance of the bone marrow was normal (Fig.3). In all animals, hemorrhagic lesions were predominant in the skin.

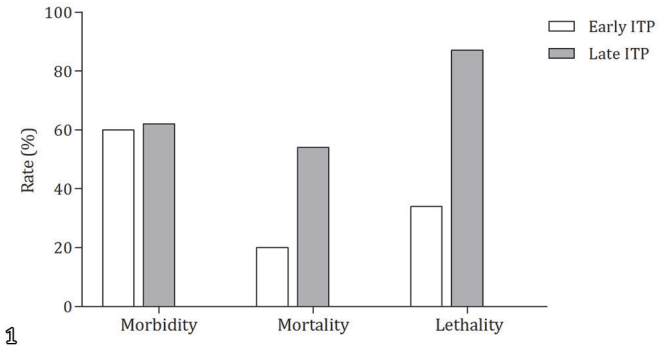

Fig.1. Rate of morbidity, mortality and lethality in piglets with early ITP (1-3 days of age, n=312) and late ITP (12-16 days of age, n=79).

Bone marrow was hypercellular with high megakaryocyte count (Fig.4) with 4±2 megakaryocytes per field at 400-fold magnification; extramedullary hematopoiesis was observed in the spleen and liver, and hemosiderophages and erythrophagocytosis were present in the epidermis, dermis, and hypodermis.

In LITP-affected animals that died (68/79), all of them had cutaneous ecchymoses in different degrees. Some piglets also presented large bruises, mainly on the face (Fig.5). Moreover, the macroscopic analysis revealed pale bone marrow in all animals (Fig.6). In 79% (54/68) of the animals, petechiae, suffusions, or ecchymoses in the heart (Fig.5), whereas 35% (24/68) of the piglets presented with ecchymoses and transmural suffusions in the small and large intestines with blood clots in the intestinal lumen. Hemorrhagic lesions in the renal pelvis, urinary vesicle, stomach, oesophagus, brain, lungs, skeletal musculature, mesentery, thymus, spleen, and lymph nodes (axillary, inguinal, submandibular, mediastinal, and mesenteric) were also observed in some animals. Microscopy showed severe medullary aplasia (Fig.7) in all LITP-affected animals (n=68), which was characterised by increased adipocytes/medullary cells ratios (>80% of the bone marrow was composed of adipocytes), and a marked decrease in megakaryocyte numbers, which were absent from ten fields examined under 400-times magnification in some marrow samples.

Additionally, histopathological analysis demonstrated hemorrhages associated with hemosiderophages and erythrophagocytosis in the epidermis, dermis, and hypodermis in

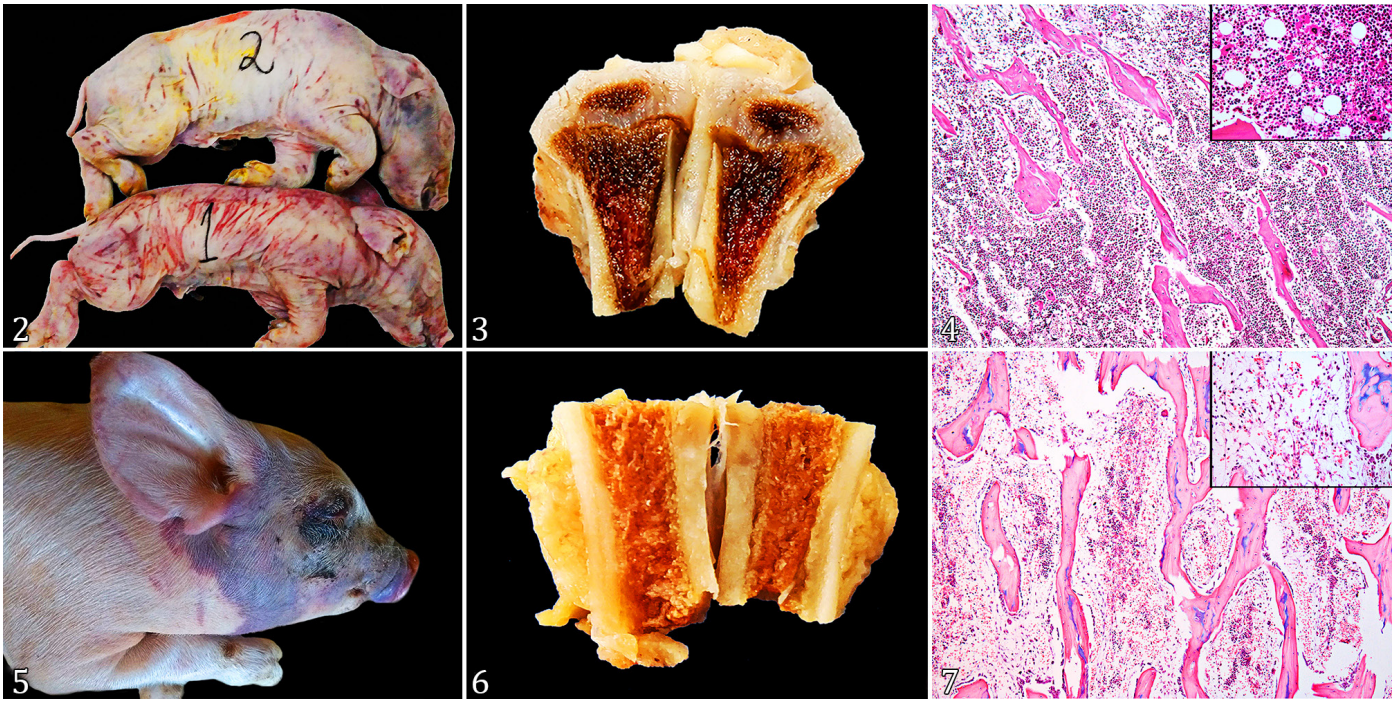

Fig.2-7. Macroscopic and histopathological findings of early (EITP, n=104) and late (LITP, n=68) isoimmune thrombocytopenic purpura. (**2**) Neonates with widespread scratches and skin bruises in EITP. (**3**) Diffuse reddish femoral bone marrow (normal macroscopic appearance) in a neonate with EITP. (**4**) Histopathology analysis of bone marrow in EITP, showing high cellularity. HE, obj.10x. Inset: presence of megakaryocytes, cells of hematopoietic lineages and few adipocytes. HE, obj.400x. (**5**) Skin, focally extensive hematoma on the face and cervical region in a piglet aged 14 days. (**6**) Medullary canal in femur with diffuse pale yellow bone marrow in piglet with LITP. (**7**) Histopathology analysis of bone marrow in LITP, showing low cellularity. HE, obj.10x. Inset: absence of megakaryocytes and low amount of cells of hematopoietic lineages. HE, obj.400x.

multifocal EITP and LITP. Hemorrhages and hemosiderophages were observed in the inguinal and axillary lymph nodes of all EITP-affected animals, as well as in the mediastinal and mesenteric lymph nodes of all LITP-affected piglets.

Hematological alterations were more severe in LITP (Table 1). Findings were mainly characterized by thrombocytopenia, lymphopenia, and eosinopenia in EITP and lymphopenia and neutropenia in LITP, respectively. Hypochromic macrocytic anemia in EITP and hypochromic microcytic anemia in LITP were also observed.

DISCUSSION

ITP is a severe hemorrhagic disease, which can present as one of two forms: EITP and LITP. Due to its acute nature, rapid diagnosis is difficult, and treatment is typically delayed. The litters affected, often have high rates of mortality (Joller et al. 2020). The results of the current study indicate mortality rates of 20% in newborn piglets (EITP) and 60% in 13-14-day-old piglets (LITP), with overall rates of 0.9% and 1.6%, respectively. In a study carried out on breeding farms in Taiwan, the overall mortality rate of piglets due to ITP reached 2.4% (Hsu et al. 2016), which is similar to our findings. However, the highest rate of mortality from PTI neonate piglets (50–70%) were observed by Joller et al. (2020) when compared to our study. This difference may be related to the number of litters evaluated and the experience of workers to perform the rapid diagnosis and treatment of affected piglets.

The pathological and hematological analyses indicated that all animals in this study (affected by either ITP form) presented with severe hemorrhagic lesions, thrombocytopenia, and severe anemia. The lesions were more severe in piglets aged 12-16 days (LITP) and mainly occurred in the intestine, heart, and skin. In thrombocytopenic animals, hemorrhagic lesions were mainly observed in organs with substantial activity, such as the intestines and the heart, or in organs with greater exposure to physical factors, such as the skin. Patterns of pathological lesions similar have also been described by (Ocarino et al. 2016, Valli et al. 2015).

Additionally, histopathological analysis revealed hypercellular bone marrow and extramedullary hematopoiesis in EITP and severe medullary aplasia in LITP. Severe hemorrhagic lesions observed in different organs and tissues were associated with thrombocytopenia resulting from an immune-mediated response against platelets in newborn piglets (EITP) and with medullary aplasia in 13-14-day-old piglets (LITP). Medullary aplasia is primarily associated with the immune-mediated lysis of megakaryocytes, also referred to as the biphasic form, and is characteristic of LITP (Saunders & Kinch 1968, Dimmock et al. 1982, Forster 2007).

In the absence of inflammatory responses in different organs and tissues, hematological patterns are important for the differential diagnosis of ITP. Thrombocytopenia was observed in all animals diagnosed with EITP or LITP (Table 1). In EITP piglets, hypochromic macrocytic anemia was observed, whereas in those with LITP, hypochromic normocytic anemia was observed. According to Valli et al. (2015), an immune-mediated response against platelets affects coagulation mechanisms, causing hemorrhagic lesions and anemia. In contrast, in cases with immune-mediated hemolytic anemia, splenomegaly, jaundice, hemoglobinuria, increased mean corpuscular hemoglobin concentration, spherocytes, agglutination, and erythrophagocytosis can be observed (Rebar et al. 2003, Thrall 2015a).

Leucopenia, mainly characterised by lymphopenia but also by eosinopenia, refers to a chronic stress leucogram seen in most piglets with EITP and is possibly associated with increased cortisol levels, which occur 4-8 hours after disease onset (Thrall 2015b). In LITP, leucopenia is more severe than in EITP and is characterized by neutropenia and lymphopenia (Saunders & Kinch 1968, Linklater et al. 1973), indicating medullary aplasia (Ocarino et al. 2016), which is supported by the histopathological results of the animals bone marrow (Fig.2).

Clinically, animals with ITP presented with dyspnea, weight loss, hyporexia, and apathy. Similar clinical findings have also been described by Stormorken et al. (1963), Linklater et al. (1973), Carrasco et al. (2003), Hsu et al. (2016) and Joller et al. (2020), possibly associated with severe anemia presented by animals with EPTI. According to Thrall (2015c), anemia and/or intense blood loss result in decreased oxygen saturation, dyspnea, muscle weakness, decreased movement and hyporexia, which may explain the clinical signs observed in our study.

Table 1. Haemotology and clinical chemistry in piglets with early ITP (1-3 days of age, n=3,) and late ITP (12-16 days of age, n=3)

Parameters	Control x̄±SD	Early ITP x̄±SD	Late ITP x̄±SD
Red blood cells (× 10^6/µL)	5.4±0.24	3.54±0.58	3.2±0.4
Haemoglobin (g/dL)	9.7±0.25	6.57±0.9	5.64±0.17
Haematocrit (%)	34±1.0	27.34±3.1	19±3.6
MCV (fL)	68.5±6.5	73.04±1.5	58.04±2.8
MCHC (%)	30.1±0.15	28.27±1.1	29.57±0.76
Platelets	655±55	72±18	18±1.3
Total leucocytes	7730±120	5433.34±450	3210±318.2
Band neutrophils (cell/µL)	0	0	0
Segmented neutrophils (cell/µL)	3470.5±29.5	2848.67±240	2634±228.2
Lymphocytes (cell/µL)	3958.5±301.5	1990.34±188	3170±282.6
Eosinophils (cell/µL)	150.5±4.5	69.34±60.8	13,34±3.1
Monocytes (cell/µL)	150.5±4.5	126±10.9	11.6±6.2
Basophils (cell/µL)	0	0	0

ITP = Isoimmune thrombocytopaenic purpura; Control group = piglets 1-12 days (n=6), x̄ = mean, SD = standard deviation.

ITP treatment was carried out by exchanging sows immediately after hemorrhagic lesions were observed. This strategy was effective for treating most EITP (208/312, 66%) cases; however, the response observed in LITP (11/79, 14%) was considerably lower because it is more severe, acute and frequently results in sudden death. Similar findings are described by (Ocarino et al. 2016, Joller et al. 2020). According by Fighera & Graça (2016), animals with medullar aplasia cannot sustain blood demand and may have severe hemorrhages and frequent death from hypovolemic shock.

CONCLUSIONS

Isoimmune thrombocytopenic purpura (ITP) is a disease that occurs in swine farms from Brazil in two clinical forms, early (EITP) and late (LITP). We found 20% and 53% of mortality in EITP and LITP, respectively.

The acute pattern, high mortality rates and urgency to differentiating ITP from other hemorrhagic diseases render rapid diagnosis essential for effective treatment and control. In this context, knowledge of the clinical-pathological, histological and hematological aspects is fundamental.

In the pathological and histopathological analysis, hemorrhagies were observed in multiple organs, more marked on the skin, heart, and intestines. Furthermore, histopathological analysis of bone marrow is important to the differentiation between LITP and EITP. According to our findings, the lesions were more severe in LITP when comparted with EITP, which is also associated with lower response to treatment in LITP.

Moreover, further studies involving the etiopathogenesis of LITP are needed to better understand this form of ITP.

Conflict of interest statement.- The authors declare having no conflicts of interest.

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