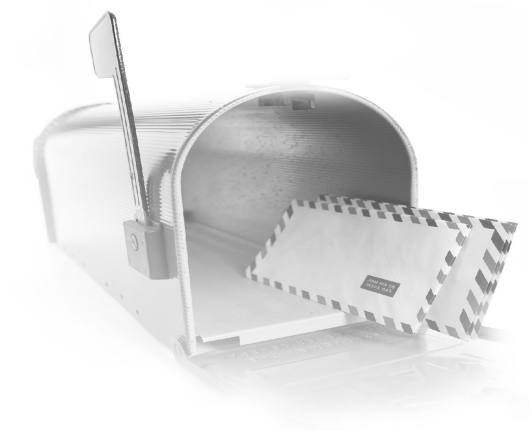

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Letters to the Editor

Lupus anticoagulant hypoprothrombinemia syndrome - could it be a sequelae of COVID-19?

TO THE EDITOR: Lupus anticoagulant hypoprothrombinemia syndrome (LAHPS) is a rare hematological entity, described in children only in a few case reports and case reports series. It was first reported in 1960, in a patient with systemic lupus erythematosus (SLE) who suffered from serious bleedings and had hypoprothrombinemia caused by an inhibitor impending prothrombin activity [1]. This acquired coagulopathy may be associated with an underlying autoimmune disease [2-6], or it may be a transient event following viral infection, particularly adenovirus [7-9]. Along with bleeding, which may be mild to life-threatening [2-4, 6, 10], typical laboratory findings are prolonged activated partial thromboplastin time (APTT), with or without prolonged prothrombin time (PT), along with positive lupus anticoagulant (LAC) and deficiency of prothrombin - factor II (FII) [1-12].

We herein present a case of a six-year-old, previously healthy girl, hospitalized at the Division of Pulmonology, Allergology, Immunology and Rheumatology, Department of Pediatrics, Children's Hospital Zagreb, Croatia due to spontaneous bruising, without other manifest bleedings, accompanied with minor swelling and soreness of the right ankle. The patient was in a good general condition, afebrile, with multiple hematomas of various phases of resorption, mainly distributed on lower extremities and back, with the largest one in the sacral area (Fig. 1). The patient and her parents denied any severe trauma. A week before, she overcame an acute, presumably viral enterocolitis, treated symptomatically at home, while four months prior to the admission she had coronavirus disease 2019 (COVID-19) infection, confirmed by PCR testing, presenting as a common cold. The patient's mother stated that the tendency to spontaneous bruising was present for a while and could chronologically be associated with the previous COVID-19 infection. At admission, rapid antigen test for COVID-19 was negative.

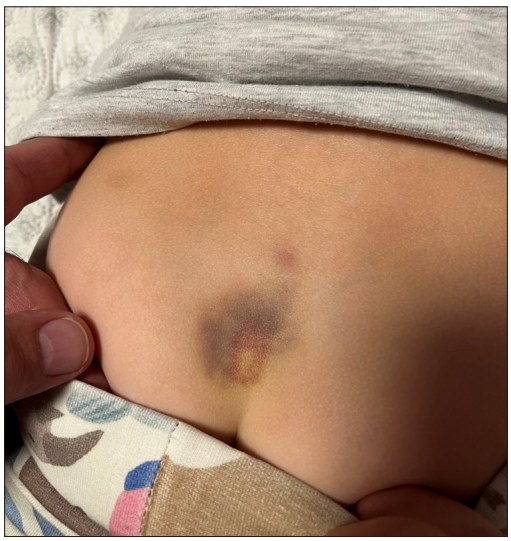

Fig. 1. A large hematoma in the sacral area.

Table 1. Laboratory findings upon admission.

Parameter	Value	Reference range
RBC	4.76×10^{12}/L	$4.00–5.00\times10^{12}$/L
Hb	125 g/L	109–138 g/L
Hct	0.380	0.320–0.404
Platelets	455×10^{9}/L	$150–450\times10^{9}$/L
WBC	8.32×10^{9}/L	$5.0–13.0\times10^{9}$/L
CRP	2.1 mg/L	0.1–2.8 mg/L
C3 complement component	0.57 g/L	0.9–1.8 g/L
C4 complement component	<0.08 g/L	0.1–0.4 g/L
Anti-COVID-19 IgM and IgG antibodies	>250 U/mL	>0.8 U/mL–positive
PV	59% activity	>70% activity
APTT	64.0 s	23–31.9 s
LA	1.49	<1.37
F II	26% activity	70–120% activity

Extensive laboratory work-up revealed a normal blood count, excluding thrombocytopenia as the cause of cutaneous bleeding, low inflammation parameters, unremarkable standard biochemistry findings (including liver synthesis markers and kidney function tests) and urine analysis. However, coagulation tests revealed prolongation of both PT and APTT, while C3 and C4 complement levels were reduced. This indicated the need for further immunological and hematological diagnostics to elucidate the underlying pathology, which confirmed the presence of LAC and a low F II activity level (Table 1). Since the patient was clinically stable during the whole hospital stay and did not develop any new bleeds, we decided to proceed with the watchful waiting approach, rather than introducing corticosteroid treatment, known to be the first line therapy for LAHPS. She was regularly evaluated; within a three-weeks period APTT (28.9 s) and PT (98% activity) normalized, as well as C3 (1.17 g/L) and C4 (0.18 g/L) complement levels. As the patient had an unremarkable family and personal medical history and no additional anamnestic data or clinical signs indicating autoimmune disease, such as SLE or antiphospholipid syndrome, the most probable diagnosis was a transient, viral-induced LAHPS. Finally, subsequent immunological testing ruled out an underlying autoimmune disease [negative antinuclear antibodies (ANA), extractable nuclear antigen (ENA) panel, antineutrophil cytoplasmic antibodies (ANCA), anticardiolipin and beta 2 glycoprotein antibodies]. The only question remaining unanswered was the exact microbial trigger to LAHPS. It might have been the acute viral enterocolitis that the patient recovered from a week before admission, but given the fact that bruises started appearing a few months before the admission, soon after the girl recovered from COVID-19 infection, COVID-19 was the more probable cause. At the time of writing this paper, our patient continues to be in a multidisciplinary follow-up, and so far, has not shown signs of disease relapse.

Clinical and laboratory features in our patient are in accordance with case reports previously published on transient, post-infective LAHPS in pediatric age group. Children usually present with mild bleeds or may be asymptomatic but have a prolonged PT and APTT, along with the presence of LAC, following acute gastrointestinal or respiratory infection. The rarity of this syndrome leaves it without formulated evidence-based treatment guidelines. Therapeutical approach is mainly conservative, as children with transient LAHPS usually show spontaneous recovery within a few weeks, including normalization of coagulation tests [7, 8]. Immunosuppressants (corticosteroids, rituximab, cyclophosphamide, azathioprine) and intravenous immunoglobulins (IVIG), combined with life-saving supportive measures (blood transfusions, fresh frozen plasma, vitamin K, recombinant factor VII and/or antifibrinolytics), are used to treat children with major clinical hemorrhages [2-5, 9, 10]. LAHPS associated with autoimmune disease is usually more persistent and more commonly complicated by severe bleeding diathesis (fatal pulmonary hemorrhage [2], bilateral adrenal hemorrhage [6], deep tissue hematomas [5]), compared to the transient post-infectious LAHPS. However, serious episodes of hematemesis and hemarthrosis, have been reported in previously healthy patients with non-SLE associated LAHPS [12].

The pathophysiological mechanism in LAHPS was first explained by Bajaj *et al.* [11] Although LAC is usually associated with thrombotic events, the authors postulated that in the case of LAHPS the presence of non-neutralizing anti-prothrombin antibodies induces rapid clearance of prothrombin antigen-antibody complexes in the reticuloendothelial system, eventually resulting in hypoprothrombinemia and bleeding diathesis. A report of one case of LAHPS in a familial infectious context speculated that there may exist a genetic predisposition to anti-prothrombin antibodies [8]. More recently, LAC-positive coagulopathy was observed in adult patients with COVID-19 infection. It presents mainly as isolated APTT prolongation, but without bleeding tendency, so the laboratory finding is not a contraindication for antithrombotic therapy [13]. However, to our knowledge, a case of a possible post-COVID-19 pediatric LAHPS has not yet been reported in the literature.

We believe that the prevalence of post-infectious LAHPS is underestimated, as there are described asymptomatic cases of transient coagulopathy, detected only due to extensive laboratory work-up in acute illness. However, in the setting of an acute respiratory or intestinal infection (especially if caused by adenovirus), followed by mucocutaneous bleeding, one must always think of LAHPS. We therefore suggest performing coagulation indices in these patients as a screening method for LAHPS to avoid rare, but possibly life-threatening hemorrhagic episodes. Depending on the severity of symptoms, watchful waiting or therapeutical approach should commence, corticosteroids being the first and usually most easily available choice. We also emphasize the importance of further regular follow-up for patients with positive LAC, particularly if combined with positive antinuclear antibodies (ANA), as LAHPS in these cases may precede or be the first manifestation of an autoimmune disease.

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CD5+ follicular lymphoma rapidly transformed to high-grade B-cell lymphoma with double-hit: from *BCL2* to *MYC* disruption

TO THE EDITOR: CD5+ follicular lymphoma (CD5+FL) is an infrequent disease that has been associated with poor prognosis and a rapid transformation to diffuse large B-cell lymphoma (DLBCL) [1, 2]. We herein describe a patient diagnosed with this entity that evolved to a high-grade B-cell lymphoma with double hit (DH-HGBCL) and appealing molecular abnormalities five months after diagnosis.

A 42-year-old male was admitted because of malaise. Blood test revealed hemoglobin 144 g/L, lactate dehydrogenase (LDH) 445 U/L (normal range, 208–378) and beta-2 microglobulin 3.90 mg/L (normal range, 1–2.40). A CT scan showed generalized lymph node enlargement. A bone marrow (BM) aspirate and biopsy showed an interstitial infiltrate of atypical lymphocytes (Fig. 1A). A lymph node biopsy showed an infiltrate of centrocytes with a follicular pattern (Fig. 1B). Immunophenotype of lymph node disaggregate was CD19+, CD10+(weak), CD20+, CD38+(MFI: 187), CD25+, FMC7+, CD5+, Bcl2+, CD45+low, CD23 negative and lambda clonality (Fig. 2). Immunohistochemistry confirmed the expression of CD5; MUM1 was negative. A normal karyotype was obtained, but FISH revealed 94% nuclei with Bcl-2 rearrangement (MetaSystems Translocation/DF Probe, Medford, MA, USA) (Fig. 1C). Bcl-6 and c-Myc were negative. FR1 and FR2 clonality was noted by using IdentiClone IGH Gene Clonality Assay (Invivoscribe Technologies, San Diego, CA, USA) (Fig. 1D). PET-CT showed increased glycidic metabolism of supra and infradiafragmatic lymph nodes (SUVmax 7.9), and diffuse increased metabolism of several bone structures (SUV 4.3). A diagnosis of CD5+FL, histology grade 2, Ann Arbor stage IV-B and either IPI 2 and FLIPI-2 3 was established. The patient was treated with O-CHOP [Obinutuzumab 1,000 mg IV infusion, administered on Day 1, 8 and 15 during Cycle 1, and on Day 1 of subsequent cycles, for 6–8 cycles; Cyclophosphamide 750 mg/m^2 IV, Doxorubicin 50 mg/m^2 IV, Vincristine 1.4 mg/m^2 (maximum 2 mg) IV on Day 1 of each 21-day cycle, and Prednisone 100 mg administered orally on Days 1-5 of each 21-day cycle for six cycles].

After 6 cycles, he was readmitted because of shortness of breath. LDH was 17,000 U/L (normal range, 208–378). Reevaluation PET-CT showed partial metabolic response in lymph nodes but pleural progressive disease and bilateral pleural effusion (SUVmax 4.6).

A new BM aspirate showed an infiltrate (15%) of great sized lymphocytes with high N/C ratio, irregularly shaped nuclei with immature chromatin and conspicuous nucleoli. Cytoplasms were hyperbasophilic and contained a number of unstained vacuolae (Fig. 1E). A thoracocentesis showed