analesdepediatría

www.analesdepediatria.org

SCIENTIFIC LETTER

Systemic lupus erythematosus of atypical onset: a presentation of 3 cases☆

Lupus eritematoso sistémico de debut atípico: a propósito de tres casos

Dear Editor:

A Dominican girl aged 10 years sought care for fever without focus, vomiting and high blood pressure with onset 1 month prior. The blood tests results were: haemoglobin (Hb), 6 g/dL; schistocytes; positive direct Coombs test; platelets, 46 000/μL; creatinine (Cr), 2 mg/dL and nephrotic-range proteinuria (protein: creatinine ratio [Pr:Cr], 6 mg/mg); antinuclear antibodies (ANA,) 1/640; anti-dsDNA antibodies, 1/1280; C3, 23.1 mg/dL and C4, 2.8 mg/dL. The patient tested negative for Shiga toxin-producing *Escherichia coli* and had normal ADAMTS13 activity. Given the suspicion of atypical haemolytic uraemic syndrome (HUS) in the context of systemic lupus erythematosus (SLE), we initiated treatment with 3 intravenous (IV) methylprednisolone pulses (500 mg) followed by oral prednisone (1 mg/kg), IV cyclophosphamide (500 mg/15 days), IV eculizumab (900 mg/week) and sessions of haemofiltration to manage the progressive deterioration of renal function and uraemic encephalopathy. Examination of a renal biopsy specimen revealed features compatible with class IV lupus nephritis with active and chronic (A/C) lesions and thrombotic microangiopathy (TMA) (Fig. 1). After 2 weeks, given the persistence of primarily haematologic activity, we added immunoglobulins (1 mg/kg) and rituximab (375 mg/m^2/week for 4 weeks, alternating every other week with cyclophosphamide). After a month's stay in hospital, the patient exhibited progressive and sustained improvement of renal function in absence of proteinuria (Cr, 0.82 mg/dL; Pr:Cr, 0.75 mg/mg) and of TMA (Hb, 11 g/dL; platelets, 378 000/μl). After completing the course of cyclophosphamide, the patient started maintenance treatment with mycophenolate (500 mg/12 h).

An Asian girl aged 8 years presented with poor general health. The salient findings of blood tests were: Hb, 8.4 g/dL; schistocytes; platelets, 11 000/μl, negative direct Coombs test; haematuria and Pr:Cr of 11 mg/mg with normal renal function; ANA, 1/640; negative anti-dsDNA test; C3, 60.9 mg/dL and C4, 12.8 mg/dL; ADAMTS13, 0% and negative anti-ADAMTS13 and genetic tests. The initial treatment consisted of IV methylprednisolone (3 boluses of 500 mg) followed by a step-down protocol of oral prednisone (1 mg/kg) and plasmapheresis. The patient exhibited a favourable haematological and renal response after 1 week of treatment, so she was discharged home. A month later, after withdrawal of steroid therapy, the patient presented with epistaxis and purpura in the lower extremities and blood tests results evincing worsening: Hb, 10 g/dL; platelets, 10 000/μl; Pr:Cr 5 mg/mg. The test for detection of anti-Ro52 antibodies was positive. Based on the suspicion of reactivation of thrombotic thrombocytopenic purpura (TTP) in the context SLE, the patient once again underwent plasmapheresis and received treatment with methylprednisolone boluses and oral prednisone at a dose of 2 mg/kg. The patient exhibited a favourable haematologic response (Hb, 11 g/dL; platelets, 178 000/μl), and the subsequent examination of a renal biopsy specimen revealed features suggestive of class V lupus nephritis, prompting initiation of maintenance therapy with mycophenolate (1 g/12 h) that achieved normalization of the protein levels in urine and ADAMTS13 activity (95%).

A Dominican boy aged 11 years presented with illness of 1 week's duration characterised by fever, aphthae, a butterfly rash, erythematous oedematous plaques in the trunk (Fig. 2A) and polyarthralgia. The salient findings of blood tests were: white blood cell count of 2000 cells/μL; Hb, 10 g/dL; positive direct Coombs test; ANA antibodies, 1/1280; anti-dsDNA greater than 1/320; C3, 18 mg/dL and C4, 1.8 mg/dL; a triple positive antiphospholipid IgE antibody profile in absence of thrombotic features (strongly positive anticoagulant lupus test; anti-B2GPI IgG, 231.7 U/mL; ACA IgG, 70 U/mL); activated partial thromboplastin time (APTT), 33 s; prothrombin percent activity (PT%), 52%; factor II, 33%; mixing study PT%, 85% indicative of factor II deficiency with no evidence of bleeding; mild haematuria; Pr:Cr, 1 mg/mg with normal renal function. The biopsy findings were compatible with acute cutaneous lupus, and the renal biopsy was postponed due to risk of haemorrhage, but it remained necessary because prognosis and treatment depend on the pathological classification of affected important organs. Treatment consisted of a step-down protocol of oral prednisone at an initial dose of 1 mg/kg and hydroxychloroquine at a dose of 200 mg/day, with clinical improvement of the skin and mucosae observed at 5 days (Fig. 2B) and normalization of coagulation (negative lupus antigoaculant test; anti-B2GPI IgG, 48 U/mL and ACA IgG, 26 U/mL; mixing study PT%, 77%; factor II, 60%) that was maintained throughout the follow-up. This allowed obtention of a renal biopsy sample the features of which were compatible with class III lupus nephritis. The patient started treatment with mycophenolate (500 mg/12 h) with normalization of urine sediment findings at 1 month. Three months later, rituximab was added (2 doses of 750 mg/m^2 14 days apart) to manage refractory cutaneous and articular activity.

☆ Please cite this article as: Barrio Nogal L, Clemente Garulo D, de Lucas Collantes C, Aparicio López C, López Robledillo JC. Lupus eritematoso sistémico de debut atípico: a propósito de tres casos. An Pediatr (Barc). 2020;93:257–259.

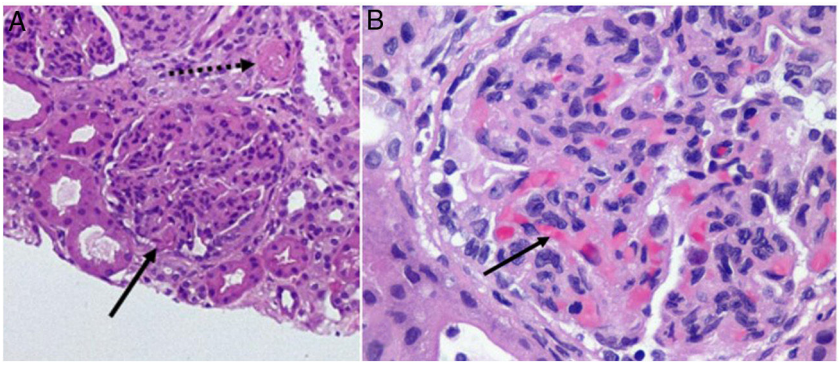

Figure 1 Renal biopsy. Haematoxylin and eosin staining. A) Hyperlobulated glomeruli with significant proliferation *(continuous arrow)*. Arteriole occluded with fibrinoid material *(dotted arrow)*. B) Occlusion of glomerular capillaries by fibrin-rich thrombi.

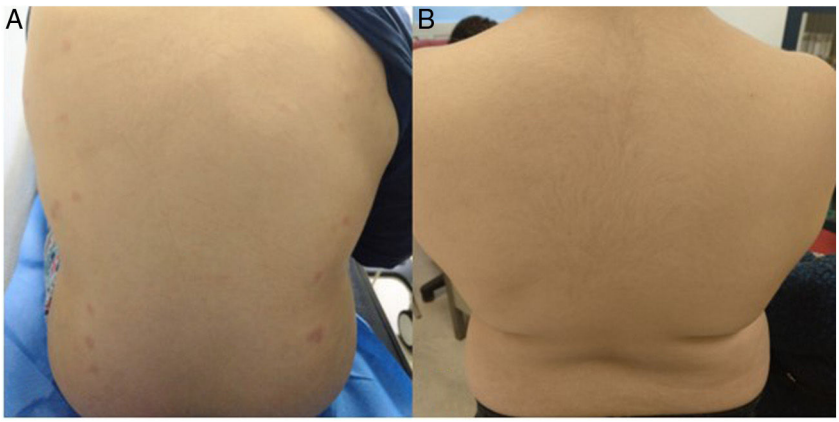

Figure 2 Erythematosquamous papules consistent with subacute cutaneous lupus erythematosus. A) At treatment initiation. B) At 1 week of treatment.

Thrombotic microangiopathies are characterised by haemolytic anaemia and thrombocytopenia with variable organ involvement. The most frequent type is HUS secondary to infection by Shiga toxin-producing *E. coli*; atypical SHU results from a dysregulation of the alternative complement pathway of genetic aetiology that is treated with eculizumab, which blocks C5 and thus inhibits formation of the membrane attack complex[1]; TTP results from a congenital or acquired deficiency of ADAMTS13 activity. Secondary MATs develop in the context of various diseases, such as disorders of connective tissues (chiefly SLE and antiphospholipid syndrome). Systemic lupus erythematosus usually predates the onset of MAT (73%).[1]

The histological classification of lupus nephritis is an important prognostic factor. In addition to the classic subtypes, it is important to assess for the presence of other lesions, among which MAT is most relevant due to having the least favourable outcomes and being an independent risk factor for kidney injury.[2] Forms associated with SLE used to be managed with immunosuppressive therapy and plasmapheresis,[1,2] but since complement activation plays a role in both disorders, eculizumab has been used in recent series of patients with lupus nephritis refractory to conventional immunosuppressive therapy, achieving good responses.[1] Other studies have reported clinical improvement and a lower cumulative steroid dose with the addition of rituximab to induction therapy, especially in black patients.[3]

The presence of TTP is associated with long duration of SLE, nephritis and high disease activity.[4] Clinical manifestations and monitoring of enzymatic activity (which is normal in remission) can guide the diagnosis in case of negative antibody test results. Patients are managed with plasmapheresis until blood work findings improve or with immunoglobulin therapy combined with high-dose steroid therapy. The addition of rituximab may be helpful in refractory cases.[4]

Lupus anticoagulant hypoprothrombinaemia syndrome (LAHS) is associated with an acquired factor II deficiency and positive lupus anticoagulant results.[5] It is most frequent in childhood[5] and predominantly associated to connective tissue disorders.[6] It is suspected in the presence of prolonged aPTT and PTT with full correction of PTT and minimal correction of the aPTT in the mixing studies.[6] It manifests with bleeding (mainly of the skin and mucosae) but may be associated with thrombosis in patients with tissue disorders (10%).[5] Treatment is based on plasma transfusions and steroid therapy alone or combined with an immunosuppressive agent depending on the systemic manifestations, which usually achieves normalization of coagulation and resolution of bleeding.[5,6] At this point, the patients should be monitored for the potential development of thrombosis with initiation of platelet antiaggregation or anticoagulation therapy if necessary.[5]

References

1. Kello N, Khoury LE, Marder G, Furie R, Zapantis E, Horowitz DL. Secondary thrombotic microangiopathy in systemic lupus erythematosus and antiphospholipid syndrome, the role of complement and use of eculizumab: case series and review of literature. Semin Arthritis Rheum. 2018. S0049-172, 30493-1.
2. Yu F, Haas M, Glassock R, Zhao MH. Redefining lupus nephritis: clinical implications of pathophysiologic subtypes. Nat Rev Nephrol. 2017;13:483–95.
3. Lehman TJ, Singh C, Ramanathan A, Alperin R, Adams A, Barinstein L, Moorthy N. Prolonged improvement of childhood onset systemic lupus erythematosus following systematic administration of rituximab and cyclophosphamide. Pediatr Rheumatol Online J. 2014;12:3.
4. Bamidele OF, Akintayo RO, Bojuwoye MO, Alabi TO, Akintayo FC, Bamidele OV. Thrombotic thrombocytopenic purpura as the first presentation in systemic lupus erythematosus. Reumatologia. 2018;56:268–70.
5. Pilania RK, Suri D, Jindal AK, Kumar N, Sharma A, Sharma P, et al. Lupus anticoagulant hypoprothrombinemia syndrome associated with systemic lupus erythematosus in children: report of two cases and systematic review of the literature. Rheumatol Int. 2018;38:1933–40.
6. Sarker T, Roy S, Hollon W, Rajpurkar M. Lupus anticoagulant acquired hypoprothrombinemia syndrome in childhood: two distinct patterns and review of the literature. Haemophilia. 2015;21:754–60.

Laura Barrio Nogal[a,*], Daniel Clemente Garulo[b], Carmen de Lucas Collantes[c], Cristina Aparicio López[c], Juan Carlos López Robledillo[b]

[a] *Servicio de Enfermedades del Sistema Inmune y Reumatología, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain*
[b] *Servicio de Reumatología Pediátrica, Hospital Universitario Niño Jesús, Madrid, Spain*
[c] *Servicio de Nefrología, Hospital Universitario Niño Jesús, Madrid, Spain*

* Corresponding author.
E-mail address: lbarrio@torrejonsalud.com
(L. Barrio Nogal).

https://doi.org/10.1016/j.anpede.2019.12.013
2341-2879/ © 2020 Asociación Española de Pediatría. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Juvenile idiopathic arthritis and Turner's syndrome☆

Artritis idiopática juvenil y síndromede Turner

To the Editor:

Turner syndrome (TS), which is associated with complete or partial monosomy of the X chromosome, is one of the most frequent and best-known chromosomal disorders. In addition to the typical features, such as short stature and amenorrhoea, affected girls are at higher risk of having other diseases compared to the general population, including autoimmune disorders. The association of TS with autoimmune thyroiditis, type 1 diabetes and inflammatory bowel disease has been solidly established, but its association with juvenile idiopathic arthritis (JIA) is not as well understood. We present the cases of 3 girls with TS and JIA managed in our hospital whose diagnosis elicited uncertainty or unnecessary treatments and the results of a literature review that confirms that while the association is infrequent, it is nevertheless well established.

The 3 patients had a 45×0 karyotype. In 2 cases, the diagnosis was made in the neonatal period, and in 1 case it was made antenatally by means of amniocentesis. All 3 patients started growth hormone replacement therapy at age 3–4 years. All 3 received the diagnosis of TS years before JIA was diagnosed, and the history of TS had not been considered significant in any of them for the purpose of referral to rheumatology.

A girl aged 7 years was referred for evaluation of monoarthritis in the left knee identified a month prior. In December 2016, the patient underwent arthrocentesis for obtention of a synovial fluid sample that had features consistent with inflammation (13 500 white blood cells [WBCs]/mm^3; 80% mononuclear cells; glucose concentration, 49 mg/dL, protein concentration, 4.8 g/dL). The patient received a diagnosis of JIA and treatment with intraarticular corticosteroids. Three months later she had a relapse in the same knee, leading to initiation of treatment with subcutaneous methotrexate (MTX), with a good response. The girl remained in remission for the following 12 months, so MTX was discontinued. After 5 months without treatment, in January 2019 the patient experienced a relapse in the left knee, leading to resumption of treatment with MTX. She is currently in remission.

The second case corresponded to a girl that had undergone surgical correction of tetralogy of Fallot that was haemodynamically stable and presented at age 5 years with arthritis in the right knee concurrent with a streptococcal infection (scarlet fever). Two weeks later she presented with arthritis in the contralateral knee and was admitted to receive intravenous antibiotherapy. She did not improve with treatment, so she was referred to the department of rheumatology for evaluation. Given the history and course of disease, with persistence of mild synovitis in the right knee, the patient received a diagnosis of oligoarticular JIA. She underwent arthrocentesis in both knees, with examination of synovial fluid revealing inflammatory features (WBC count, 9500 cells/mm^3; 80% polymorphonuclear cells; glucose, 52 mg/dL, protein concentration, 5.3 g/dL). The patient received intraarticular corticosteroids and exhibited a partial response, which prompted initiation of subcutaneous MTX. She is currently in remission. The third patient was a girl aged 6 years with a personal history of monoarthritis in the right knee and a previous arthrocentesis that had revealed inflammatory features in the synovial fluid (WBC count, 8700 cells/mm^3; 60% mononuclear cells; glucose concentration, 66 mg/dL, protein concentration, 5.2 g/dL). She was referred to the department of rheumatology and given a diagnosis of oligoarticular JIA in January 2019. She has been treated with intraarticular corticosteroid injections and is currently in remission without treatment.

All 3 patients had negative results of tests for detection of antinuclear antibodies (ANA), rheumatoid factor (RF) and HLA-B27 antigen. None had associated uveitis or other autoimmune disorders.

☆ Please cite this article as: Lavilla P, Manzanares Á, Rabadán E, de Inocencio J. Artritis idiopática juvenil y síndromede Turner. An Pediatr (Barc). 2020;93:259–261.