REFERÊNCIAS

1. Instituto Nacional de Estatística. Censos 2011 [Consultado 2012 Nov 28] Disponível em: http://censos.ine.pt/xportal/xmain?xpid=CENSOS&xpgid=censos2011_apresentacao.
2. Ministério da Saúde, Direcção Geral da Saúde. Programa Nacional para a Saúde das Pessoas Idosas. Lisboa: DGS; 2004. [Consultado 2012 Nov 28] Disponível em: http://www.min-saude.pt/NR/rdonlyres/1C6DFF0E-9E74-4DED-94A9-F7EA0B3760AA/0/i006346.pdf.
3. Delirium, demência, perturbações mnésicas e outras perturbações cognitivas. In Manual de diagnóstico e estatística das perturbações mentais. 4ª ed. Lisboa: Climepsi editores; 2006.
4. Hejl A, Høgh P, Waldemar G. Potencially reversible conditions in 1000 consecutive memory clinic patients. J Neurol Neurosurg Psychiatr. 2002;73:390-4.
5. Rigo JC, Rigo JF, Faria BC, Santos VM. Demência reversível e quedas associadas ao biperideno. Rev Psiq Clín. 2006;33:24-7.
6. Robles Bayón A, Gude Sampedro F. Prescripciones inconvenientes en el tratamiento del paciente con deterioro cognitivo. Neurología. 2012 (in press).
7. Campbell N, Boustani M, Limbil T, Ott C, Fox C, Maidment I, et al. The cognitive impact of anticholinergics: A clinical review. Clin Interv Aging. 2009;4:225–33.
8. Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. BMJ. 2006;332:455-9.
9. Carrièrre I, Fourrier-Reglat A, Dartigues JF, Rouaud O, Pasquier F, Ritchie K, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. Arch Intern Med. 2009;169:1317–24.
10. Rojas-Hernandez CH, Cameron JCF. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. Ann Pharmacother. 2012;46:549-57.
11. Jiménez-Jiménez FJ, Puertas I, de Toledo-Heras M. Drug-induced myoclonus: frequency, mechanisms and management. CNS Drugs. 2004;18:93-104.

Tubulointerstitial Nephritis and Uveitis Syndrome with non Caseating Granuloma in Bone Marrow Biopsy

Nefrite Tubulointersticial e Uveíte com Granulomas não Caseosos na Biópsia Óssea

Maria FRAGA[1], Maria João NUNES DA SILVA[1,2], Margarida LUCAS[1,2], Rui M. VICTORINO[1,2]

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ABSTRACT

The Tubulointerstitial Nephritis and Uveitis syndrome is a very rare condition, probably under-diagnosed in clinical practice. It is characterized by the combination of an interstitial nephritis and uveitis, and is an exclusion diagnosis. Tissue non caseating granuloma can be rarely present, with only 6 cases reported on bone marrow. We present a case of a 55 year old female with a 3-month history of asthenia and weight loss. Blood tests showed anemia and renal insufficiency. Renal biopsy revealed interstitial nephritis and the bone marrow biopsy showed caseating granuloma. One month later anterior uveitis of the left eye appeared. An extensive exclusion of all possible causes allowed a diagnosis of Tubulointerstitial Nephritis and Uveitis syndrome with caseating granuloma in bone marrow. As ocular and renal manifestations may not occur simultaneously, Tubulointerstitial Nephritis and Uveitis Syndrome should be systematically considered in cases of interstitial nephritis and/or uveitis, and tissue granulomas can be part of this rare syndrome.

Keywords: Bone Marrow; Granuloma; Uveitis; Nephritis, Interstitial.

RESUMO

A Síndrome nefrite túbulo intersticial e uveíte é uma síndrome rara e provavelmente sub-diagnosticado na prática clinica. É caracterizada pela ocorrência de nefrite intersticial e de uveíte, sendo um diagnóstico de exclusão. Granulomas não caseosos nos vários tecidos são raros, estando descritos apenas seis casos de granulomas não caseosos na medula óssea. Apresentamos um caso de uma mulher de 55 anos, com quadro de três meses de evolução de astenia e emagrecimento. Laboratorialmente apresentava anemia e insuficiência renal. A biopsia renal revelou nefrite intersticial e a biópsia da medula óssea mostrou granulomas não caseosos. Um mês depois surgiu uveíte anterior do olho esquerdo. A exclusão de todas as possíveis etiologias permitiu o diagnóstico final de Síndrome nefrite túbulo intersticial e uveíte com granulomas não caseosos na medula óssea. Considerando que as manifestações oculares e renais podem não ocorrer simultaneamente, a Síndrome nefrite túbulo intersticial e uveíte deve ser sistematicamente equacionada em doentes com nefrite intersticial e/ou uveíte, podendo os granulomas fazer parte desta rara patologia.

Palavras-chave: Granuloma; Medula Óssea; Nefrite Intersticial; Uveíte.

INTRODUCTION

The TINU (Tubulointerstitial Nephritis and Uveitis) Syndrome was described in 1975[1] and approximately 200 cases have since been reported worldwide.[2] It is an exclusion diagnosis, probably under-diagnosed in clinical practice, characterized by the combination of an interstitial nephritis (IN) and uveitis, which may not occur simultaneously. The uveitis is generally anterior, bilateral and in 65% of the cases arising after the IN.[3] Non caseating granulomas (NCG) were found in 13% of the renal biopsies, but granulomas in bone marrow (BM) had only be described in 6 cases.[1] Patients may present fever, weight loss, anorexia, asthenia, abdominal pain or flank pain, arthralgia and myalgia. Laboratory features include anaemia, increased erythrocyte sedimentation rate (ESR),

1. Serviço de Medicina 2. Hospital de Santa Maria. Centro Hospitalar Lisboa Norte. Lisboa. Portugal.
2. Faculdade de Medicina. Universidade de Lisboa. Lisboa. Portugal.

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renal failure (RF) and mild proteinuria.[3,4] The IN has usually a good prognosis, can remit either spontaneously or with corticoid therapy. The uveitis also responds favorably to steroids (local or systemic), but recurrence or chronicity may occur.[3,5] In cases that were not responsive to steroids immunomodulatory agents including methotrexate, cyclosporine, azathioprine and mycophenolate mofetil have been used successfully.[6] We describe a case of TINU Syndrome with NCG at the BM.

CLINICAL CASE

A 55 year-old female, hypertensive and diabetic, was admitted in Emergency Service with a 3-month history of asthenia, anorexia, 12 Kg weight loss and oliguria in the 15 days before. She denied fever or ingestion of drugs, namely NSAIDS. There was a marked anemia (hemoglobin 7.6 g/dl, VGM 78 fl), RF (creatinine 3.8 mg/dl, urea 108 mg/dl), ESR 83 mm and C reactive protein 7.8 mg/dl; Urinalysis showed proteinuria and leucocyturia and 24 hours urine protein excretion was 1285 mg. The patient had normal laboratory assessment prior to the beginning of complaints. Renal ultrasonography showed kidneys of dimensions in the upper limit of normal. Blood and urine cultures, including those for tuberculosis were negative, as well as IGRA test; Serological tests for Hepatitis, VIH, CMV, EBV and Herpes simplex, Syphilis, *Brucella* and *Toxoplasma gondii* and autoimmune markers (ANA,ENA, ANCA, anti-ds-DNA antibody and rheumatoid factor) were negative. Immunoglobulins and complement factors were normal. Chest X-ray was normal and chest, abdominal and pelvic CT showed only multiple adenopathies along carotid, jugular, spinal chains and in jaw topography, some at the upper limit of normal. The BM biopsy revealed a normocellular marrow with two non necrotizing epithelioid granulomas (Fig. 1). Renal histology was consistent with tubulointerstitial nephritis with inflammatory infiltrate comprised by lymphocytes, plasmocytes and neutrophils (Fig. 2). Red blood cells transfusion and hydration were done, and the patient was discharged with hemoglobin 9.4 g/dl and creatinine 1.7 mg/dl. Three months later the patient still had asthenia and anorexia and anterior uveitis of the left eye appeared and laboratory evaluation showed hemoglobin 10.7 g/dl, creatinine 1.96 mg/dl and ESR 89 mm. The presence of IN, uveitis and NCG in BM justified bronchoscopy. Bronchoalveolar lavage was normal, post-bronchoscopy expectorated sputum was negative for viral, bacterial and *Mycobaterium Tuberculosis* studies and lung biopsy was normal. The 24 hours calciuria and angiotensin-converting enzyme were normal as well as Gallium scintigraphy. The exclusion of different possible etiologies from this clinical picture led to the diagnosis of TINU syndrome with a rare form of bone marrow involvement,

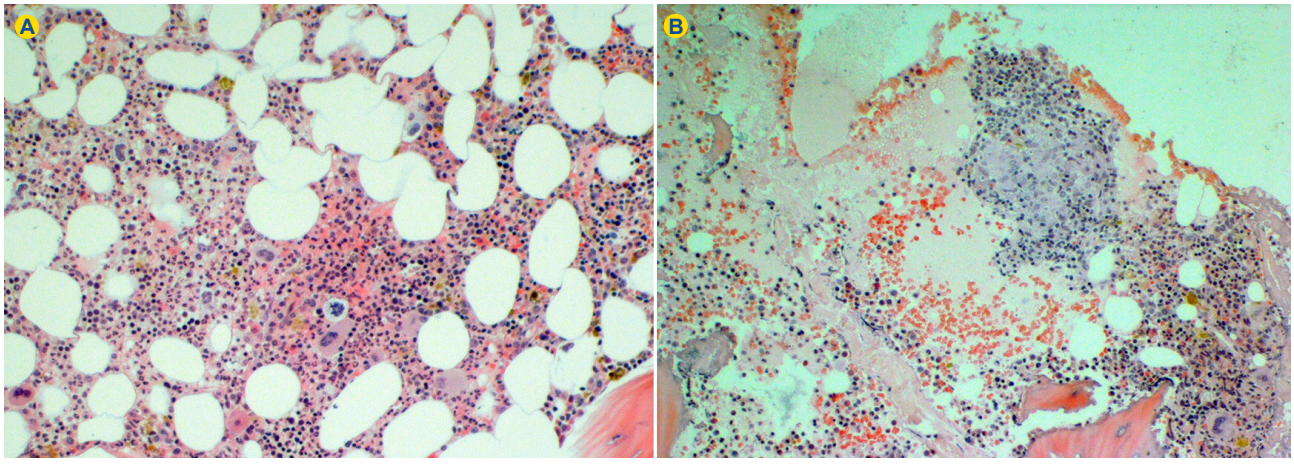

Figure 1- Bone marrow biopsy: (A) normocellular marrow. (B) bone marrow with non necrotizing epithelioid granuloma.

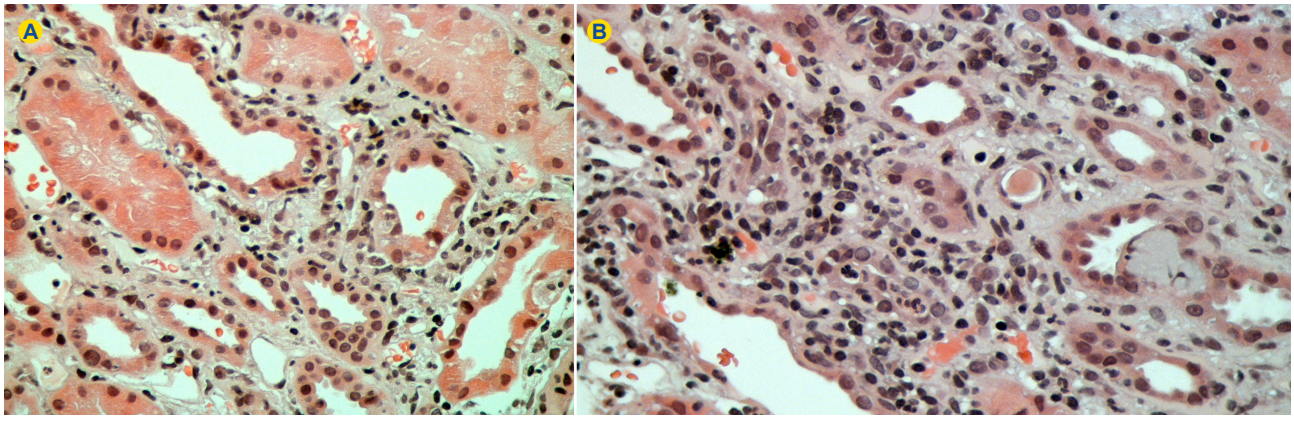

Figure 2 - Renal Biopsy: tubulointerstitial nephritis with inflammatory infiltrate comprised by lymphocytes, plasmocytes and neutrophils.

associated to severe anemia. Oral prednisolone (0.8 mg/kg/day) was initiated and tapered to zero over 6 months, with normalization of renal function, hemoglobin and ESR. Five months later she had relapse of uveitis of left eye, with resolution with topical steroid. Currently, 2 years after the diagnosis of TINU syndrome, the patient remains asymptomatic without steroid therapy, with creatinine of 0,85 mg/dl, hemoglobin of 12.5 g/dl and ESR of 14 mm.

DISCUSSION

TINU syndrome is a very rare condition, probably underdiagnosed in clinical practice and is an exclusion diagnosis. The present case was characterized by the association of IN, uveitis and NCG in the BM, which represent an extremely rare event. An extensive exclusion of all possible alternatives causes allowed a final diagnosis of TINU syndrome with NCG in BM. It is important to remember that ocular and renal manifestations may not occur simultaneously, as occurred in our patient, leading to a particularly difficult establishment of a diagnosis in these cases. On the other hand mild renal disease sometimes does not become symptomatic and diagnostic tests regarding renal involvement are not performed at the time of presentation of uveitis.[7,8] This could be the basis for this disease being underdiagnosed in clinical practice.

The pathogenesis of this syndrome is not yet clear although possible association to drug exposure (like NSAIDS and antibiotics), infections and autoimmune diseases has been suggested.[3,9] It is thought that autoimmune mechanisms involving T-cell mediated hypersensitivity could play a large role in this disorder.[10] Some studies have described that helper/inducer T cells subset predominates in the renal interstitial infiltration in TINU, hypothesizing that this CD4+ T cells cellular-immune response mediated could lead to the formation of granuloma.[10-12] More recently, a high prevalence of modified C-reactive protein (mCRP) was identified in renal and ocular tissues in patients with TINU syndrome, along with autoantibodies against mCRP.[13] This study suggests that mCRP may be one of the common target autoantigens in renal and ocular tissues for patients with TINU syndrome, although further studies are needed to prove that mCRP autoantibodies are pathogenic in this disease.[13] In Conclusion, as ocular and renal manifestations may not occur simultaneously, TINU Syndrome should be systematically considered in cases of NI and/or uveitis, and tissue granulomas can be part of this rare syndrome.

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CONFLICTS OF INTEREST

The authors have no competing interests to declare.

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REFERENCES

1. Dobrin R, Vernier R, Fish A. Acute eosinophilic interstitial nephritis and renal failure with bone Marrow-Lymph node granulomas and anterior uveitis. A new syndrome. Am J Med. 1975;59:325-33.
2. Venugopal P, Damodaran S, Stocks R. A case of tubulointerstitial nephritis and uveitis (TINU) syndrome. Arch Dis Child. 2012;97:A165.
3. Mandeville J, Levinson R, Holland G. The tubulointerstitial nephritis and uveitis syndrome. Surv Ophthalmol. 2001;46:195-208.
4. Bento V, Castro I, Batista J, Mesquita J. TINU syndrome – two clinical cases of tubulo-interstitial nephritis and uveitis. Port J Nephrol Hypert. 2008;22:263-6.
5. Thomassen V, Ring T, Thaarup J, Baggessen K. Tubulointerstitial nephritis and uveitis (TINU) syndrome: a case report and review of the literature. Acta Ophthalmol. 2009;87:676-9.
6. Herlitz LC, Chun MJ, Stokes MB, Markowitz GS. Uveitis and acute renal failure. Kidney Int. 2007;72:1554-7.
7. Izzedine H. Tubulointerstitial nephritis and uveitis syndrome (TINU): a step forward to understanding and elusive oculorenal syndrome. Nephrol Dial Transplant. 2008;23:1095-7.
8. Mackensen F, Smith JR, Rosenbaum JT. Enhanced recognition, treatment, and prognosis of tubulointerstitial nephritis and uveitis syndrome. Ophthalmology. 2007;114:995-9.
9. Sinnamon K, Courtney A, Harron C, Rourke D, Mullan R. Tubulointerstitial nephritis and uveitis (TINU) syndrome: epidemiology, diagnosis and management. Nephrol Dial Transplant. 2008;2:112-6.
10. Abed L, Merouani A, Haddad E, Benoit G, Oligny L, Sartelet H. Presence of autoantibodies againts tubular and uveal cells in a patient with tubulointerstitial nephritis and uveítis (TINU) síndrome. Nephrol Dial Transplant. 2008;23:1452-5.
11. Tanaka H, Suzuki K, Nakahata T, Tateyama T, Waga S, Ito E. Repeat renal biopsy in a girl with tubulointerstitial nephritis and uveitis syndrome. Pediatr Nephrol. 2001;16:885-7.
12. Yano N, Miyazaki M, Endoh M, Kuramoto T, Eguchi K, Yagame M, et al. Idiopathic acute interstitial nephritis associated with uveitis. Jpn J Med. 1991;30:548-52.
13. Tan Y, Yu F, Qu Z, Su T, Xing G, Wu L, et al. Modified C-reactive protein might be a target autoantigen of TINU syndrome. Clin J Am Soc Nephrol. 2011;6:93.

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Av. Almirante Gago Coutinho, 151
1749-084 Lisboa, Portugal.
Tel: +351 218 428 215
E-mail: submissao@actamedicaportuguesa.com
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