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Paclitaxel-induced lupus glomerulonephritis

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Abstract

Introduction : Paclitaxel is a pharmaceutical molecule belonging to the taxane family of antimitotic agents, which act by blocking the disassembly of microtubules. Among the rare side effects of this chemotherapy is induced lupus, responsible for the generation of autoantibodies and a clinical presentation less severe than that of systemic lupus erythematosus.
Observation : We report the case of a 69-year-old patient treated 20 years ago for pulmonary tuberculosis and bilateral bronchial adenocarcinoma treated with neoadjuvant Paclitaxel and Carboplatin-based chemotherapy. She was admitted following the discovery of advanced renal failure 6 months after her 3rd course of treatment for glomerular nephropathy syndrome. A renal biopsy showed class IV (A/C) lupus proliferative glomerulonephritis. Immunological tests (AAN, native DNA, Sm, SSa, SSb) were negative, and the C3 fraction of complement was consumed. This suggests systemic lupus with renal tropism and secondary Gougerot Sjögren's syndrome. Treatment consisted of induction therapy with corticoids and Cyclophosphamide. Progression was favourable with Rituximab-based maintenance therapy.
Discussion: The pathophysiological mechanisms of induced lupus are not clearly defined, and many predisposing factors are known. Therapeutic management is essentially based on recognition and discontinuation of the incriminating molecule.
Conclusion: Renal involvement is exceptional in induced lupus. Several predisposing factors are known, mainly genetic. Therapeutic management is that of systemic lupus erythematosus.

Keywords

Paclitaxel, Lupus, Glomerulonephritis

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Main Article

Introduction:

Paclitaxel is a molecule widely used in oncology, mainly for the treatment of breast, lung and ovarian cancer. It is a member of the taxane family of antimitotics, which act by blocking the disassembly of microtubules. One of the rare side effects of this chemotherapy is induced lupus. Induced lupus refers to drug reactions caused by certain agents such as ACE inhibitors, beta-blockers and calcium channel blockers, which are responsible for the generation of autoantibodies and a clinical picture less severe than that of systemic lupus erythematosus. The most frequently suggested mechanism is inappropriate immune activation following drug exposure in a genetically predisposed patient. We report the case of a 69-year-old female patient who had received Paclitaxel-based chemotherapy for bronchial adenocarcinoma, and was admitted for management of renal failure leading to the discovery of lupus glomerulonephritis, to highlight the clinico-biological presentation of this entity, its evolution and the importance of recognizing the incriminating molecule.

Observation:

This is a 69-year-old patient treated 20 years ago for pulmonary tuberculosis with chronic obstructive pulmonary disease sequelae, followed for 15 years for type 2 diabetes complicated by moderate non-proliferative diabetic retinopathy and bronchial adenocarcinoma (two masses, left and right) treated with neoadjuvant chemotherapy based on Paclitaxel (175 mg/m²) and Carboplatin (400 mg/m²) in 3 courses, followed by left lobectomy. The patient was admitted following the discovery of advanced renal failure 6 months after her 3rd course (creatinine level at 33 mg/L, or GFR at 15 mL/min/1.73m² according to CKD-EPI), with a glomerular nephropathy syndrome consisting of arterial hypertension, microscopic hematuria and nephrotic proteinuria at 4.35 g/24H. A right renal biopsy was performed. Light microscopy revealed two cortico-medullary biopsy cores. They contained 17 glomeruli, including 3 in Pain à cacheter (PAC). 7 glomeruli showed endocapillary hypercellularity and extracapillary proliferation with active epithelial crescents. 7 glomeruli showed isolated endocapillary hypercellularity. 3 glomeruli also showed signs of glomerulosclerosis, with images of flocculocapsular synechia. The interstitium was marked by inflammatory fibrosis estimated at 70% of the surface area examined, composed of non-specific mononuclear elements, sometimes with a follicular appearance. The tubes were atrophic in the areas of fibrosis, with the presence of hyaline cylinders and hematic cylinders. In addition, tubular necrosis covering 30% of the

cortical surface was noted. The vessels were marked by arteriolar hyalinosis and moderate fibrous endarteritis. On immunofluorescence, a biopsy core containing 9 glomeruli was received. Intense, diffuse, global parietal and mesangial deposition of granular IgG, C3 and C1Q was demonstrated, with trace mesangial IgM and Kappa, as well as weak, segmental, focal mesangial fibrinogen deposition. The histological and direct immunofluorescence appearance was that of proliferative glomerulonephritis with signs of chronicity, compatible with lupus nephropathy class IV (A/C) according to the ISN/RPS 2018 classification.

In the immunoassay, the C3 fraction of complement was consumed at 0.79 g/L, while the C4 fraction was at 0.35 g/L. Anti-nuclear antibodies, anti-nuclear cell autoantibodies (ANCA), anti-DNA antibodies and anti-soluble nuclear antigen antibodies were all negative. The patient also underwent an ophthalmological consultation, where dry eyes and macular atrophy were identified. A biopsy of the salivary glands was carried out, which came back in favour of Chisholm and Mason grade 3 chronic lymphocytic sialadenitis. In conclusion, we found a systemic lupus with renal tropism of the proliferative glomerulonephritis class IV (A/C) type, with secondary Gougerot Sjögren's syndrome. Therapeutic management consisted of induction treatment with corticoids and Cyclophosphamide; Hydroxyplaquenil was contraindicated in view of the macular atrophy. Progress was favorable (creatinine level 17 mg/L, GFR 32 mL/min/1.73m^2) and the patient was put on Rituximab maintenance therapy.

Discussion:

Although the pathophysiological mechanisms of induced lupus are not clearly defined, several predisposing factors are known, including genetic predisposition. Certain phenotypes were found, such as HLA BW44 in chlorpromazine-induced lupus, and HLA DQA1*0501 in the case of sulfasalazine (1). Inducing agents can act through an action on DNA, either by inhibiting methylation, thus activating the transcription of certain genes leading to autoimmune disease (2), or by denaturing nucleoproteins, transforming DNA into a more immunogenic type (3). Another metabolism involved is the alteration of apoptosis and the accumulation of debris, leading to the emergence of an autoimmune process.

In the study by Velove et al. 90% of patients with induced lupus had arthralgias and 50% had myalgias. Skin involvement, fever and serous effusions were less frequent than in lupus erythematosus, and central nervous system and renal involvement were exceptional. Moreover, antinuclear antibody levels, present in 95% of cases with a predominance of anti-histone antibodies, gradually regressed with resolution of induced lupus (4).

This rare pattern of renal involvement is similar to the study by Gunnarsson et al. of 41 patients with rheumatoid arthritis treated with sulfasalazine monotherapy for over 6 months. 4 patients developed induced lupus, including 2 who developed anti-native DNA antibodies after 12 months' treatment, and one patient whose kidney biopsy after 26 months showed lupus class V glomerulonephritis (5).

On the other hand, in the series by Alarcón-Segovia et al. involving 50 patients who developed reactions attributable to induced lupus after taking Hydralazine-based antihypertensive therapy, 10 patients developed renal involvement, 8 with moderate to severe proteinuria and 7 with microscopic hematuria (6).

Therapeutic management of induced lupus is essentially based on recognition and discontinuation of the offending drug (7). NSAIDs and corticosteroids have been used in some cases for short periods in patients with moderate symptoms. In refractory cases, and in cases of severe visceral damage, immunosuppressive agents may be considered (8).

Conclusion:

Renal involvement during induced lupus is exceptionally described. The onset of clinical signs after prescription of the inducing drug varies from a few weeks to 2 or even 3 years, and therapeutic management is that of systemic lupus erythematosus.

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