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# Danazol-induced Acute Pulmonary Fibrosis in a Patient with Idiopathic Thrombocytopenic Purpura: Could Anti Fibrosant Therapy be Useful?

**René Agustín Flores-Franco[1*], Víctor Alejandro Salgado-Yáñez[1], Jesús Rivera-Olivas[1] and Ernesto Ramos-Martínez[2]**

*[1]Hospital Christus Muguerza Del Parque, Calle Dr. Pedro Leal y de la Llave. Col. Centro, CP 31000, Chihuahua, Chih., México.*
*[2]Patología e Inmunohistoquimica de Chihuahua, S.C. Calle Gómez Farías 115, Col. Centro, CP 31000, Chihuahua, Chih., México.*

***Authors' contributions***

*All authors contributed to the realization of the manuscript. Author RAFF was the attending physician and who designed the manuscript. Author VASY reviewed the clinical aspects of the manuscript. Author JRO was the hematologist in charge and who diagnosed and treated the ITP of the patient. Author ERM was the pathologist who worked and revised the slides of lung biopsies of the patient. Each author has read the final manuscript and approved all statements in it.*

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***Case Study***

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## ABSTRACT

**Introduction:** Danazol is frequently used in the treatment of idiopathic thrombocytopenic purpura (ITP). Very occasionally are described in the elderly fatal respiratory complications related to this drug such as acute pulmonary fibrosis for which no treatment has proven to be effective. **Presentation of Case:** We describe a case of an old man with ITP treated with danazol who developed a pulmonary fibrosing disease not attributed to any other cause. Damaged lung reversed using an anti fibrosant therapy approved for other types of pulmonary fibrosing diseases. **Discussion and Conclusion:** Pulmonary fibrosing disease attributed to danazol is a condition refractory to systemic corticosteroids, but as shown in the present case, an anti fibrosant therapy has proven to be a useful alternative and could be recommended in the light of current knowledge.

**Corresponding author: E-mail: rflores99@prontomail.com;*

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## 1. INTRODUCTION

Danazol is a weak synthetic androgen frequently used in the treatment of Idiopathic thrombocytopenic purpura (ITP) specially in elderly patients in whom first-line alternatives pose a risk [1] Some adverse events produced by this drug are mood or menstrual changes, hirsutism, rash, myalgias, and transaminase elevations. Very occasionally are described respiratory complications, mainly acute pulmonary fibrosis, bronchiolitis obliterans organized pneumonia (BOOP), and hypersensitivity pneumonitis [2-5]. Reported fibrosing forms showed an unsuccessful response to systemic corticosteroids and their results were fatal [2-3]. We report the first case of acute pulmonary fibrosis attributed to danazol therapy in an old man with ITP who responded satisfactorily to an antifibrotic therapy.

## 2. PRESENTATION OF CASE

A 78-year old man was admitted for evaluation of ecchymosis in the lower extremities associated to a blood platelet count of 20 x $10^9$/l. The bone marrow aspiration was consistent with ITP therefore he was started on therapy including danazol 400 mg daily and prednisone 100 mg daily in decreasing doses. A few days later a significant increase in platelet count was observed, but it was also accompanied of a white cell count of 19.1 x $10^9$/l, with no obvious infectious cause. Two months after starting this treatment he was hospitalized again because he had experienced fatigue, weakness, and dyspnea for 6 days. On admission her vital signs were a blood pressure of 90/60, heart rate of 116 beats per minute, respiratory rate of 26 breaths per minute, and a temperature of 99.6ºF. Chest auscultation revealed fine rales in both lungs. Cardiac sounds where rhythmic, without murmurs or a galloping rhythm. Arterial blood gases, breathing supplementary oxygen via a mask, showed pH 7.50, $PaO_2$ 50 mmHg, $PaCO_2$ 21 mmHg, $SatO_2$ 88.5%, lactate 3 mmol/L, $HCO_3^-$ 16.2 mEq/L. Chest radiography showed diffuse interstitial opacities (Fig. 1B) and in the computed tomography (CT) these images corresponded with a ground glass pattern (Fig. 2A). Laboratory findings: Hemoglobin 15 g/dl, white blood count 23.16 x $10^9$/l, neutrophils 21.9 x $10^9$/l, platelet count 246 x $10^9$/l, glucose 113 mg/dl, creatinine 3.8 mg/dl, urea 149 mg/dl, uric acid 9.2 mg/dl, ureic nitrogen 69.9 mg/dl, aspartate aminotransferase 69 mg/dl, alanine aminotransferase 142 mg/dl, lactic dehydrogenase 1,396 mg/dl, sodium 146 mmol/L, potassium 4.7 mmol/L, chloride 106 mmol/L. Further studies included a thyroid profile and cardiac enzymes were within normal ranges. Also, HVB, HVC, HIV, antinuclear antibodies, p-ANCA, c-ANCA, blood and urine cultures all showed negative results. Despite the use of broad-spectrum antimicrobials and systemic corticosteroids, his respiratory failure and leukocytosis persisted. A transbronchial lung biopsy showed interstitial fibrosis without evidence of granuloma or microorganisms (Fig. 2B). Failing to find any underlying cause we decided to discontinue danazol therapy. After eleven days the patient consented be discharged to his home with supplementary oxygen, decreasing doses of prednisone 50 mg every third day, and the empirically use of long acting pirfenidone 100 mg BID, and n-acetylcysteine 900 mg daily. The patient slowly showed a clinic, functional and radiologic improvement (Fig. 1C) and 4 months later, both the medication and supplemental oxygen were discontinued.

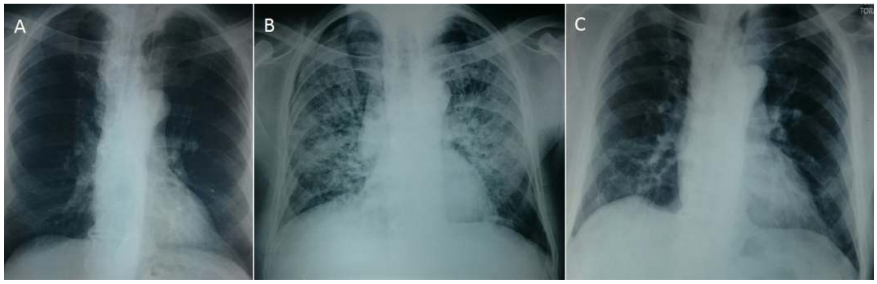


**Fig. 1. Chest radiographs at different moments of the progression of the pulmonary fibrosing disease. In A, during the initial diagnosis of ITP; in B, when the patient is in acute respiratory failure; and C, four months after danazol was suspended**

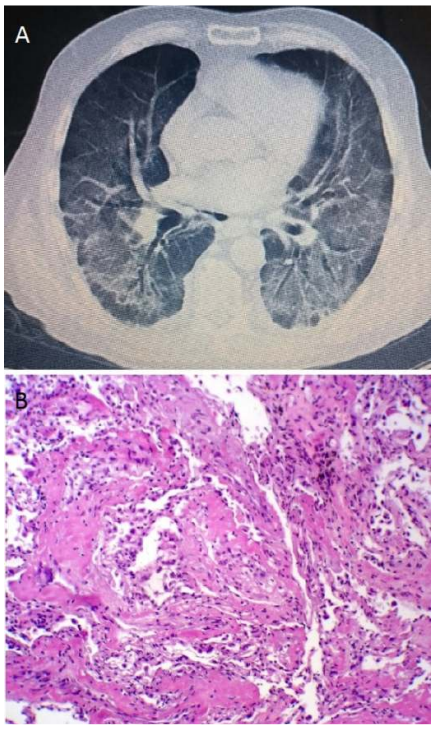


**Fig. 2. A, chest CT showed ground glass images in both lungs. B, biopsy obtained by bronchoscopy revealing hyalinized focal lung fibrosis with hyperplasia of type II pneumocytes**

## 3. DISCUSSION

The management of ITP in the older people can be difficult, taking into account the comorbidities, the concomitant medication and the adverse events of treatments [1]. Usually the treatment with danazol is well tolerated. Mechanism of action of danazol is not well known, but it has been hypothesized that, in addition to stimulating the bone marrow, it might improve cytopenias by decreasing the number of the Fcγ receptors. In a retrospective study of elderly patients with ITP, the most common adverse events of danazol were moderate to severe elevation of serum aspartate or alanine aminotransferase levels, defined as between 2 and 10-fold higher than normal values [6]. Our patient developed a rare respiratory complication non related to another cause or exposition. Also, we did not find any infectious cause of the leukocytosis, but this appears as soon as we initiated danazol so we consider it as the possible cause. The only two cases reported of pulmonary fibrosis related to danazol therapy has been described in adults over 70 years old after 6-12 weeks of initiating the treatment and when the concomitant use of systemic corticosteroids were in tapering doses [2,3]. The doses of danazol used were 600 mg and 100 mg respectively. Both cases had a catastrophic result even though they were treated with high doses of systemic corticosteroids and cyclophosphamide [2,3].

The lung biopsy did not oriented us towards any subtype of fibrosant lung disease and based on the poor results observed with systemic corticosteroids, we empirically use an anti fibrosant therapy, which however to the date still have not proved a long-term favorable effects on survival of patients with idiopathic pulmonary fibrosis (IPF) [7]. This is a devastating, progressive and irreversible disease with limited therapeutic options and is considered the most investigated disease towards the application of an anti fibrosant therapy. Even less research exists about the effectivity of an anti fibrosant therapy in other fibrosing lung diseases. Small research conducted in patients with secondary pulmonary fibrosis treated with N-acetylcysteine has shown beneficial results compared to those receiving corticosteroids and azathioprine [8]. Waiting for more evidence, we still decided to use this treatment as we note a poor response to systemic corticosteroids. Our results could be encouraging, however must be corroborated in randomized trials.

## 4. CONCLUSION

Pulmonary fibrosis attributed to danazol use, although rare, is a potentially fatal condition unresponsive to only discontinuation of the drug and the use of systemic corticosteroids. Waiting for more research, an anti fibrosant therapy approved for other types of fibrosant lung diseases seems effective and its use should be seriously considered, seeing the ineffectiveness of other treatments.

## CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES


1. Mahévas M, Michel M, Godeau B. How we manage immune thrombocytopenia in the elderly. Br J Haematol; 2016. DOI: 10.1111/bjh.14067
2. Pakhale S, Moltyaner Y, Chamberlain D, Lazar N. Rapidly progressive pulmonary fibrosis in a patient treated with danazol for idiopathic thrombocytopenic purpura. Can Respir J. 2004;11:55-7.
3. Grange MJ, Dombret MC, Fantin B, Gougerot-Pocidalo MA. Fatal acute pulmonary fibrosis in a patient treated by danazol for thrombocytopenia. Am J Hematol. 1996;53:149.
4. Sill JM, Regn D, Marks D, Morris M. A case of bronchiolitis with organizing pneumonia in a patient treated with danazol for idiopathic thrombocytopenia purpura. Chest 2008, annual meeting abstracts. Case reports posters. Abstract ID 1094363.
5. L'Huillier JP, Quinquivel ML, Desrues B, et al. Le danazol: Une nouvelle etiologie de pneumopathie d'hypersensibilité. Rev Mal Respire. 1990;7:106.
6. Andres E, Zulfiqar AA, Serraj K, Zimmer J, Vogel T, et al. Idiopathic thrombocytopenic purpura in elderly patients: A two center retrospective study of 41 cases. J Blood Disord Transfus. 2015;6:278.
7. Idiopathic pulmonary fibrosis clinical research network, Martinez FJ, de Andrade JA, Anstrom KJ, King TE Jr, Raghu G. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2093-2101.
8. Estrada A, Carrillo G, Buendía I, Mejía M, Selman M. Coadjuvant use of n-acetylcysteine in treatment of secondary pulmonary fibrosis. Chest 2011, annual meeting abstracts. Interstitial lung disease posters. Abstract ID 1119.




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