

## Casi clinici

# Late onset clozapine-induced sierositis: the case of ms C.

## *Sierosite a esordio tardivo indotta da clozapina: il caso della signora C.*

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**SUMMARY. Introduction.** Polisierositis is a rare but not negligible adverse event of a therapy with clozapine, that occurs usually during the titration phase of clozapine or just after the reachment of the plateau, and polytherapy increases the incidence rate. **Case report.** Ms. C. is a 42 years old smoker woman who suffers from a schizophrenia associated to a borderline personality disorder. In 2007 a therapy with clozapine was introduced with good tolerance and efficacy on her symptoms for a long period. In August 2015, after a period characterized by many psychiatric ward admissions an augmentation with valproic acid and sertraline was done, with partial symptoms improvement. In June 2016, she developed pleuritis and pericarditis and underwent pleural and pericardial drainage. After clozapine interruption (and zuclopentixol titration) the symptoms progressively decreased and in August 2016 she had a complete remission. **Conclusions.** Even if uncommon, sierositis should be taken into consideration also in long term clozapine treatment, especially when associated with other drugs, as valproate or sertraline, although the role of the latter is less clear. Moreover, patients life habits (smoke), allergic or rheumatological disorders or temporary intake of other drugs (like antifungins) should be recorded carefully for their possible effects on cytochrome P450 substrates.

**KEY WORDS:** clozapine, adverse event, pleuritis, pericarditis.

**RIASSUNTO. Introduzione.** La polisierosite è una rara ma non trascurabile complicanza della terapia con clozapina, che avviene solitamente nella fase di titolazione del farmaco, o appena dopo il raggiungimento del plateau, e la politerapia ne aumenterebbe il tasso di incidenza. **Caso clinico.** La sig.ra C. è una paziente di 42 anni, fumatrice, affetta da schizofrenia associata a un disturbo di personalità borderline. Nel 2007 è stata impostata una terapia con clozapina, efficace nel lungo periodo e ben tollerata dalla paziente. Nell'agosto 2015, dopo un periodo caratterizzato da numerosi accessi in Reparto, sono stati aggiunti acido valproico e sertralina, con parziale beneficio. Nel giugno 2016, la paziente ha sviluppato pleurite e pericardite ed è stata sottoposta a drenaggio pleurico e pericardico. Dopo la sospensione della clozapina (con titolazione del zuclopentixolo) i sintomi sono regrediti progressivamente e nell'agosto 2016 la paziente era in remissione completa. **Conclusioni.** Sebbene sia un evento raro, la sierosite dovrebbe essere presa in considerazione quale effetto a lungo termine del trattamento con clozapina, specialmente se associato ad altri farmaci come l'acido valproico o la sertralina, sebbene il ruolo di quest'ultima sia meno chiaro. Inoltre, dovrebbero essere segnalate attentamente le abitudini di vita (come il fumo), eventuali allergie o disturbi reumatologici o temporanea assunzione di altri farmaci (come gli antifungini) per i loro possibili effetti sui substrati del citocromo P450.

**PAROLE CHIAVE:** clozapina, eventi avversi, pleurite, pericardite.

## INTRODUCTION

Clozapine is an antipsychotic drug with significant serotonergic (5HT<sub>2</sub>), adrenergic ( $\alpha$ 1 and  $\alpha$ 2), muscarinic and histaminic (H1) blocking properties, which efficacy involves both positive and negative symptoms of schizophrenia, even in 25-30% of drug resistant patients<sup>1</sup>.

Despite this, lifethreatening agranulocytosis, which incidence is 1% can limit its use. In addition, clozapine has a dose-dependent risk of epileptic seizures (about 5% at a daily dose of 600 mg or more); potentially massive weight gain; possible cardiac damage, including early myocarditis ( $\leq$ 19 per 10 000) or late cardiomyopathy ( $\leq$ 10 per 10 000)<sup>2</sup>.

The discontinuation due to side effects is up to 17% of cases<sup>3</sup>.

The most frequent adverse events include agranulocytosis<sup>4</sup>, but inflammatory syndrome with serosal involvement is of particular interest.

A recent review carried out by Mouaffak et al.<sup>5</sup>, studied 22 patients (11 women and 11 men) who developed inflammation of 1 or more serous membrane under clozapine). The authors concluded that the development of polysierositis occurred usually during the titration phase of clozapine or just after the reachment of the plateau.

In 25% of cases clozapine was combined with valproic

acid and in 14% with sertraline. The incidence of myocarditis in clozapine-treated patients is supposed to be between 0.7% and 1.2%<sup>6</sup>, with a risk of developing myocarditis 10,000 times higher than in the general population. The association with valproic acid doubles the risk, especially in the first month of augmentation<sup>7,8</sup>.

## CASE REPORT

Ms. C. is a 42 years old smoker woman who suffers from a schizophrenia associated to a borderline personality disorder. The clinical history was silent for hypertension, diabetes or any somatic disorder. Her mother suffered from bipolar disorder and her father was alcohol addicted. The onset of her illness was at 23 years old, after a relationship separation with symptoms of paranoid delusions, anxiety, depersonalization, derealization, somatization, social retirement, feelings of unsuitableness, self devaluation, failure ideas and fluctuating depression. Since 2000, she has been in care in the outpatient clinic, alternating periods of relapse and periods of partial remission; for almost 1 year she worked in an insurance company without any erotomanic or paranoid ideation. Since summer 2005, she has reported many inpatient psychiatric ward admissions and a long psychiatric community admission and she no longer reached remission not being able to work again. During these years, she was prescribed several antidepressants, mood stabilizers, often in polytherapy. Since 2007 she has been swallowing clozapine with good tolerance and efficacy on her symptoms. In August 2015, after another relationship separation she was admitted to a psychiatric ward for worsening of agitation, paranoia, logorrhea, and obsessive thoughts. An augmentation with valproic acid and sertraline was done, with symptoms improvement. In that period, she reduced the number of cigarettes from 20 to 5-10/day. In March 2016 she was admitted at the psychiatric community for another rehabilitation period. Her pharmacotherapy consisted on clozapine 400 mg/day, zuclopentixol 20 mg/day, valproic acid 800 mg/day, sertraline 100 mg/day. After 3 months she had fever (up to 38°) and chest pain; The clinical chest examination show decreased sound in the left lung, the laboratory tests showed leukocytosis (12.10) with neutrophilia (9.64) e monocytosis (0.98) and high erythrocyte sedimentation rate (ESR) (47) and the chest radiography showed pleural effusion in lateral and back location, with enlarged heart, especially in left ventricle.

She started a therapy with ciprofloxacin and at day 6 she repeated the laboratory test which showed a further increase in white blood cell count (12,87) and in particular of monocytes (2.03) and of the ESR (50) and underwent echocardiogram, that showed a moderate pericardial effusion with increased inflammation indexes. The patient was thus admitted to the cardiac care unit and Acetylsalicylic acid 100 mg was started with early benefit on symptoms and body temperature. On day 7, the new laboratory test showed hypoalbuminemia and persistence of leukocytosis (13.80) with neutrophilia, monocytosis and proteinuria; clozapine was discontinued while the dose of zuclopentixol was increased. On day 10 after a worsening of breathing, the patient underwent a pericardiocentesis and 700 milliliters of light red fluid, containing red blood cells, many granulocytes, no malignant cancer cells, was drained. The arterial blood gas showed a mild respiratory alkalosis. The white blood cells count was still high, although slightly decreased (12.88) along with high inflammation index (reactive C protein 19.13). Antinuclear antibodies were slightly positive (1/80) while all the other investigated IGM

antibodies (for virus or bacteria) and the blood, pleural and pericardial cultural examination for mycobacteria, aerobe and anaerobe bacteria were all negative as well as rheumatoid factor, thyroid and celiac disease indexes.

On day 12 a new echocardiogram was performed showing an almost complete remission of the pericardial effusion.

On day 15 she reported an increase of pain and of inflammation indexes; an augmentation with colchicine was prescribed. A new chest radiography showed a worsening of the pleural effusion. She underwent chest biopsy and 500 milliliters of fluid containing rare red blood cells, lymphocytes, granulocytes, mesothelial cells and macrophages, without malignant cancer cells were drained out of the pleural space. She then had a progressive reduction in symptoms and improvement of the clinical picture. At day 35, she was readmitted in the psychiatric community. She had leg oedemas (white blood cells count 10,68; serum proteins 7.2) with low albumin/globulins ratio (0.67). On August 4<sup>th</sup> she did new laboratory tests. The white cell count was normal 7.52 with only a mild monocytosis (0.87); the serum proteins were still low (7.3; albumin/globulins ratio (0.76). With a rich albumin diet associated with antidiuretic therapy (furosemide) the leg oedemas remitted progressively and up to the middle of August the patients had a complete remission of the symptoms. The control laboratory tests performed on August 18<sup>th</sup> showed a normal ESR (14), normal white cells count (7.07) and mildly high but significantly reduced reactive C protein (2.54).

## DISCUSSION

Serositis is a rare phenomenon that can be caused by several conditions like myocardial infarction, uremia, metastasis, rheumatoid arthritis, systemic lupus erythematosus, viral/bacterial/protozoan/fungal infections. Even if uncommon, serosites might also be an adverse event in clozapine treatment. The pathogenesis is still uncertain: Kortner et al.<sup>9</sup> and Stanislav and Gonzales Blanco<sup>10</sup> hypothesized an allergic aetiology (IGE) of this rare phenomenon while Mouaffak et al.<sup>5</sup> and by Dauner et al.<sup>11</sup>, hypothesized a link with a comorbid infective or rheumatoid disorder. Kane and O'Neill<sup>12</sup> reported an associated increase in liver enzymes. However, in our case, the serositis was accompanied by neutrophilia, monocytosis and not by eosinophilia and despite a (mild) positive antinuclear antibody, all the other antibody indexes were negative and liver enzymes were normal. Moreover, a quick clozapine suspension was not accompanied by a quick symptoms remission, and the white blood cells remained high for almost one month and drainage of pleura and pericardium were both necessary. As in previous case reports<sup>13,14</sup>, the late onset serositis was associated to polytherapy, although sodium valproate and sertraline had been prescribed at low-medium doses.

Polytherapy should be avoided in patients with clozapine: Cadeddu et al.<sup>15</sup> observed the use of inhibitors or other substrates of cytochrome P450, such as antifungals and oral contraceptives, can increase clozapine blood levels and cause long-lasting interactions and clozapine toxicity as well. De Berardis et al.<sup>8</sup> reported a case of a 31-year old treatment-resistant male patient with schizophrenia who developed a sudden pericarditis after the introduction and titration of clozapine in the presence of an ongoing valproate regimen.

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Markovic et al.<sup>16</sup> explained a case of a 21-year-old man with psychotic disorder who had been on low dose clozapine therapy for five months (after failure of atypical antipsychotic agents) and on sertraline low doses for four months. Even after several months of politherapy, pericardial and pleural effusion started. A possible explanation of a delayed onset of sierositis might be linked to the try of smoking quitting and the reduced amount of nicotine in her body associated with valproic acid could have increased the clozapine blood concentration, through the glucuronidation of the cytochrome P4501A2, as suggested by Diaz et al.<sup>17</sup>, while the role of sertraline is less clear: 17 patients in therapy with clozapine received additional either paroxetine or sertraline and no significant changes in plasma concentrations of clozapine and its major metabolites were observed after 3 weeks of combined therapy with sertraline<sup>18</sup>.

### LIMITS

The clozapine induced sierositis can be hypothesized, but several factors contribute to the clinical picture, and must be taken into consideration and the etiology of her pericarditis remain unclear; moreover, laboratory test and chest radiography were not performed just after the augmentation with valproic acid and sertraline; the augmentation with both sertraline and valproic acid did not help us to understand which augmented drug could explain the sierositis onset.

### CONCLUSIONS

At the light of our case and previous case reports, sierositis should be taken into consideration also in long term clozapine treatment, especially when associated with other drugs, as valproate or SSRIs. Moreover, patients life habits (smoke), allergic or rheumatological disorders or temporary intake of other drugs (like antifungins) should be recorded carefully for their possible effects on cytochrome P450 substrates and clozapine dose should be adjusted, after monitoring of clozapine blood concentration.

*Conflict of interest:* the authors declare that there is no conflict of interest.

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