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 politherapy increases the incidence rate. **Case report.** Ms. C. is a 42 years old smoker woman who suffers from a schizophrénia 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 (andzuclopentixol 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 rheum atological disorders or temporary intake of other drugs (like antifungins) should be recorded carefully for their possible effects on cytochrome P450 substrates.

**INTRODUCTION**

Clozapine is an antipsychotic drug with significant serotonergic (5HT2), adrenergic (α1 and α2), muscarinic and histaminic (H1) blocking properties, which efficacy involves both positive and negative symptoms of schizophrenia, even in 25-30% of drug resistant patients1.

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 (≤19 per 10 000) or late cardiomyopathy (≤10 per 10 000)2.

The discontinuation due to side effects is up to 17% of cases3. The most frequent adverse events include agranulocytosis4, but inflammatory syndrome with serosal involvement is of particular interest. A recent review carried out by Mouaffak et al.3, 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 polyserositis 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 myocardi-
tis in clozapine-treated patients is supposed to be between
0.7% and 1.2%6, 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 augmentation24.

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 somat-
ie disorder. Her mother suffered from bipolar disorder and her fa-
ther 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, fail-
ure ideas and fluctuating depression. Since 2000, she has been in
care in the outpatient clinic, alternating periods of relapse and pe-
riods of partial remission; for almost 1 year she worked in an in-
surance company without any erotomaniac 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 im-
provement. In that period, she reduced the number of cigarettes
from 20 to 5-10/day. In March 2016 she was admitted at the psy-
chiatric community for another stabilization period. Her phar-
macotherapy 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 showed decreased sound in the left lung, the laborato-
ry 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 re-
peted the laboratory test which showed a further increase in
white blood cell count (12.87) and in particular of monocyties
(2.03) and of the ESR (50) and underwent echocardiogram,
that showed a moderate pericardial effusion with increased in-
flammation indexes. The patient was thus readmitted to the cardia
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 hypoaalbuminemia and persistence of
leukocytosis (13.80) with neutrophilia, monocytosis and protein-
uria; clozapine was discontinued while the dose of zuclopentixol
was increased. On day 10 after a worsening of breathing, the pa-
tient underwent a pericardicocentesis and 700 milliliters of light
red fluid, containing red blood cells, many granulocytes, no malign-
ant 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 inflam-
mation 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 peri-
cardial culture examination for mycobacteria, aerobe and anaer-
obe bacteria were all negative as well as rheumatoid factor, thy-
roid 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 inflam-
ination indexes; an augmentation with colchicine was pre-
scribed. 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, linfocytes, granulocytes,
mesothelial cells and macrofaghs, without malignant cancer cells
were drained out of the pleural space. She then had a progress-
ive reduction in symptoms and improvement of the clinical
picture. At day 35, she was readmitted in the psychiatric com-
munity. She had leg oedemas (white blood cells count 10.68;
serum proteins 7.2) with low albumin/globulins ratio (0.67). On
August 4th 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 antiinuetic 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 Au-
gust 18th showed a normal ESR (14), normal white cells count
(7.07) and mildly high but significantly reduced reactive C pro-
teine (2.54).

DISCUSSION

Sierositis is a rare phenomenon that can be caused by sev-
eral conditions like myocardial infarction, uremia, metastasis,
rheumatoid arthritis, systemic lupus erythematosus, viral/bacterial/protozoan/fungal infections. Even if uncom-
mon, sierositis might also be an adverse event in clozapine
treatment. The pathogenesis is still uncertain: Kortner et al.5
and Stanislaw and Gonzales Blanco10 hypothesized an aller-
gic aetiology (IGE) of this rare phenomenon while Mouaff-
fak et al.3 and by Dauner et al.11, hypothesized a link with a
comorbid infectival or rheum atoid disorder. Kane and
O’Neill12 reported an associated increase in liver enzymes.
However, in our case, the sierositis was accompanied by neu-
trophilia, 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 accompa-
nied 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 reports13,14, the late onset sierositis 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.13 observed the use of inhibitors or other sub-
strates of cytochrome P450, such as antifungals and oral con-
traceptives, can increase clozapine blood levels and cause
long-lasting interactions and clozapine toxicity as well. De
Berardis et al.8 reported a case of a 31-year old treatment-re-
sistant 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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127
Markovic et al. 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 polithrapy, 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., 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.

**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 could have increased the clozapine blood concentration, through the glucuronidation of the cytochrome P4501A2, as suggested by Diaz et al., 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.

**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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**REFERENCES**