

Clozapine-Induced DRESS Syndrome: A Case Series From the AMSP Multicenter Drug Safety Surveillance Project

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Key words

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an infrequent, but severe, adverse drug-induced reaction which occurs due to massive T-cell stimulation resulting in cytotoxicity and eosinophil activation and recruitment. The incidence is 0.4 cases per 100,000 in the general population; the mortality rate is up to 10%. Therefore, we believe that recognizing this syndrome is of particular importance. The problem we notice is that DRESS is often seen and described in patients receiving rheumatologic or anticonvulsant drugs, but very rarely in psychiatric hospitals, where Clozapine is frequently used, and that is the importance of this paper. DRESS Syndrome must be recognized promptly, and causative drugs withdrawn. Indeed, it has been reported that the earlier the drug withdrawal, the better the prognosis. In this paper, we present three cases of Clozapine-induced DRESS. All cases were recorded in the Multicenter Drug Safety Surveillance Project (AMSP).

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an infrequent but severe adverse drug-induced reaction, which occurs due to massive T-cell stimulation and results in cytotoxicity and eosinophil activation and recruitment [1]. It is associated not only with immunological factors but also with genetic predisposition. Individual susceptibility, type of drug used, titration rate, and concomitant medication play a part in the development of the reaction. The incidence is 0.4 cases per 100,000 in the general population; the mortality rate is up to 10% [2]. Therefore, we believe that recognizing this syndrome is of particular importance. Mortality cases were mainly caused by multiple organ failure and sepsis. Therapeutic management mostly includes removal of a drug, symptomatic management, life support, and use of corticosteroids [3]. In a systematic review, 44 drugs were found to be associated with 172 cases of DRESS syndrome reported between January 1997 and May 2009. The drugs reported to have caused a DRESS were inter alia aromatic and non-aromatic antiepileptic drugs (e. g., phenytoine, carbamazepine, oxcarbamazepine, lamotrigine, phenobarbital) as well as allopurinol and sulfonamides. Anticonvulsants accounted for one-third of the drugs causing DRESS. In contrast, the vast majority of the various other drugs were only associated with 1 case of DRESS [2]. The diagnosis of DRESS is very challenging because the clinical features, types of skin reactions, and organs involved may notably differ between the individuals concerned. A delayed onset of symptoms 2–6 weeks after beginning of drug administration is one of the features of DRESS [2]. A score system called RegiSCAR has been developed by an international study group investigating severe cutaneous reactions in order to define the syndrome more accurately (SCAR) [4]. For the diagnosis of DRESS, 3 of the 6 main RegiSCAR criteria have to be met: acute rash, fever above 38 °C, lymphadenopathy at

minimum 2 locations, involvement of at least 1 internal organ, and abnormalities in lymphocyte and eosinophil counts. Additional criteria include hospitalization due to the reaction. A Japanese consensus group has developed a second set of criteria for DRESS. The diagnosis requires meeting 7 of the 9 criteria in this system or all of the first 5: a maculopapular rash development > 3 weeks after drug initiation, clinical symptoms continuing > 2 weeks after stopping therapy, fever > 38 °C, liver abnormalities (ALT > 100 IU/L) or other organ involvement, leukocytosis, atypical lymphocytes, eosinophilia, lymphadenopathy, or HHV-6 reactivation [5].

This study focuses on cases in which DRESS was observed as adverse drug reaction of clozapine. So far, to our knowledge only 1 DRESS case report with involvement of clozapine was published. Ben-Ari et al. [6] described a case of a 27-year-old male with paranoid schizophrenia who was hospitalized with all 3 diagnostic criteria of DRESS syndrome as well as unusual fever pattern of high temperatures in the morning hours and lower temperatures toward evening under clozapine therapy (► **Table 1**).

Case reports

We present 3 cases of clozapine-induced DRESS. All cases were recorded in the pharmacovigilance project Arzneimittelsicherheit in der Psychiatrie (AMSP).

Case 1

A 73-year-old male patient was admitted to the Department of Psychiatry due to an acute exacerbation of a chronic paranoid schizophrenia from which he had suffered since 1970. He was treated with quetiapine up to 600 mg per day; clozapine up to 400 mg per day was added 19 days later. (The reason for this rather unusual combination was ex post not to elucidate.) Other medications administered were finasteride, tamsulosine, acetylsalicylic acid, and zopiclone. These drugs had been given for a

longer time prior to admission and were continued unchanged during hospitalization. On the 20th day of clozapine therapy, standard blood tests showed massive C-reactive protein (CRP) elevation of 24.7 mg/dL (reference range: 0–1 mg/dL). Over the next 13 days, eosinophils increased to a maximum of 1.917/nL (reference range: 0.05–0.250/nL). Moreover, the patient developed clinically severe sickness with body temperature of maximum 39 °C and somnolence. There was no infection found. Clozapine levels were in the toxic range (1683 ng/mL, dose 400 mg), and CRP was still increased (14.2 mg/dL). All drugs were discontinued, and due to the severity of the patient's health state, he was transferred to the hospital for internal medicine and treated with prednisolone. Eight days later a skin exanthema became apparent while he was already on prednisolone. A comprehensive diagnostic evaluation found no infectious or autoimmune cause. In the dismissal report, the cause of elevated liver enzymes, intermittent fever, and eosinophilia was stated as most likely a DRESS triggered by clozapine, despite initial absence of skin changes. Echocardiography showed low pericardial effusion, indicating additional mild cardiac involvement. With prednisolone therapy, a full recovery from DRESS was achieved. No immediate antipsychotic treatment was necessary afterward. Four months later, a re-exposure was tried with up to 25 mg clozapine per day, under which the patient developed an increase in CRP with discrete eosinophilia. After discontinuation of clozapine, within 2 days a clear laboratory-chemical improvement was noticed. As this represents a positive re-challenge reaction, this case was rated as definite clozapine-induced DRESS with eosinophilia, fever, rash, and increased transaminases fulfilling all 4 RegiSCAR criteria.

Case 2

A 69-year-old female patient was admitted to the Department of Psychiatry due to acute exacerbation of a paranoid schizophrenia, from which she had suffered since 1970. She was a nonsmoker. At the time of admission, laboratory routine parameters were without pathological findings. The patient was treated with up to 200 mg clozapine per day in monotherapy. On day 22 of clozapine treatment, she displayed gener-

alized edema, most pronounced in the facial area (excluding the mouth) and on all extremities, partly with slight livid discoloration and beginning scaly; she complained of a subjective "flu feeling." Eosinophilia (2.59 ng/mL), elevated liver enzymes (alanine aminotransferase: 129 U/L, reference level: <35 U/L; aspartate aminotransferase: 46 U/L, reference level: <35 U/L; gamma glutamyltransferase: 144 U/L, reference level: <40 U/L; alkaline phosphatase: 292 U/L, reference range: 42–141 U/L), and a mild increase in CRP (7 mg/L, reference range: 0–1 mg/L) were detected on the same day. The patient was transferred to a hospital for internal medicine for observation. There, she was diagnosed with DRESS under clozapine, and the drug was discontinued on day 28. Levocetirizine was given for some days. Clinical and laboratory symptoms normalized 18 days after onset of DRESS. Unfortunately, there were no serum levels of medication documented. The patient was treated with aripiprazole later on. This case was rated as a probable case of DRESS due to clozapine. With dermatologic symptoms, eosinophilia, and increased liver enzymes as organ involvement, 3 of the 4 RegiSCAR criteria were met.

Case 3

A 57-year-old female patient with schizoaffective disorder was admitted for the 12th time to the Department of Psychiatry with symptoms of depression, such as feelings of emptiness and worthlessness, acoustic hallucinations, and paranoid delusions. Furthermore, the patient was addicted to low-dose benzodiazepines. After 2 weeks, she was treated with sertraline up to 150 mg/day. Clozapine was added 18 days later and titrated up to 200 mg/day. The patient had formerly been treated with clozapine and with several different antipsychotic drugs. Lorazepam was successfully discontinued within 4 weeks. Besides, she had been taking metformin 100 mg, metoprolol 50 mg, atorvastatin 10 mg, amiloride/hydrochlorothiazide 5/50 mg, lithium carbonate 450 mg, pantoprazole 20 mg, and L-thyroxin 88 µg for a long time prior to admission, and these drugs were continued in unchanged dosage. Routine blood tests, in particular liver enzymes, were in the normal range on admission day and remained so for the first 8 weeks. However, on day 36 of

the clozapine treatment, liver enzymes started to increase and were massively elevated by day 49 (alanine aminotransferase: 1511 U/L, reference level: <35 U/L; aspartate aminotransferase: 932 U/L, reference level <35 U/L; gamma glutamyltransferase: 292 U/L, reference level <40 U/L). On day 5 of clozapine therapy, the blood level of clozapine was already rather high in relation to the given dosage: 728 ng/mL. For reasons unknown *ex post*, in this regard no action was taken. On day 49, the clozapine blood level was in the toxic range: 1551 ng/mL (reference level: 350–600 ng/mL). Furthermore, the patient had elevated CRP: 17.4 mg/dL (reference level: <0.5 mg/dL) without any clinical sign of an infection. On day 49 an exanthema was documented on both arms and hands with conflating plaques. Dermatological examination judged it to be a potentially life-threatening reaction, and a prednisolone therapy was prescribed with 0.5 mg/kg. Leucocytes and eosinophils were in the normal range (7.8/nL, 1 % eosinophils); body temperature reached a maximum of 37.5 °C. No lymphadenopathy was documented. Both clozapine and sertraline were simultaneously discontinued on day 49 of the clozapine therapy, and the patient was treated with electroconvulsive therapy further on. Five weeks after discontinuation of clozapine, liver enzymes and CRP were within normal range and the cutaneous reaction had abated. The case was rated as a probable adverse drug reaction in the sense of an incomplete clozapine-induced DRESS. With elevated liver enzymes and skin reaction as leading symptoms, the patient had 2 most common DRESS symptoms [2], but no eosinophilia, fever, and lymphadenopathy. An alternative explanation would be a sertraline-induced DRESS, which was marked as a possible alternative. However, immunological reactions are much more often side effects of clozapine than of sertraline, and DRESS has not been reported with sertraline so far (► **Table 2**).

Conclusion

So far to our knowledge, there is only 1 case report in the literature that describes DRESS in patients being administered clozapine therapy. Ben-Ari et al. have described 1 case report of a DRESS in a patient receiving clozapine and phenytoine, in

► **Table 1** RegiSCAR criteria and criteria of the Japanese consensus group represented through our cases.

RegiSCAR criteria	Criteria of the Japanese consensus group	Case 1	Case 2	Case 3
Fever > 38 °C	Fever > 38 °C	Positive	Unknown	Negative
Enlarged lymph nodes	Lymphadenopathy	Unknown	Unknown	Unknown
Eosinophilia	Eosinophilia	Positive	Positive	Negative
Atypical lymphocytes	Atypical lymphocytes	Unknown	Negative	Negative
Skin rash	Maculopapular rash development	Positive	Positive	Positive
Internal organ involvement	Liver abnormalities	Positive	Positive	Positive
	Leukocytosis	Positive	Negative	Positive
	Clinical symptoms continuing > 2 weeks after stopping therapy	Positive	Positive	Positive
	HHV-6 reactivation	Unknown	Unknown	Unknown

► **Table 2** Case 3: liver enzymes, CRP, and medications (dosage and blood levels).

Day of clozapine treatment		1	5	44	49	50	53	66	85	111
	Reference levels									
Clozapine dosage		6.25 mg	200 mg	175 mg	Pause	Pause	Pause	Pause	Pause	Pause
Clozapine level (ng/L)	350–600	-	782	-	1551	-	432	-	-	-
Clozapine DM (ng/mg)		-	271	-	336	-	157	-	-	-
ALT (U/L)	< 35	22	194	-	1511	1413	1076	102	23	14
AST (U/L)	< 35	21	144	-	932	836	414	42	18	18
GGT (U/L)	< 40	23	58	-	292	279	287	289	119	55
Sertraline dosage		50 mg	150 mg	150 mg	Pause	Pause	Pause	Pause	-	-
CRP mg/dL	< 0.5	-	5.14	-	17.4		1.93	< 0.5	-	-

which both drugs were quickly discontinued. The antiepileptic phenytoine was suspected to cause the DRESS, so clozapine was restarted, but a few days later, the patient's condition deteriorated further, and clozapine was discontinued again [6].

We present 3 additional cases. In 2 cases RegiSCAR criteria for a DRESS were met. In the third case, an incomplete DRESS was documented. In our first case, clozapine was assessed to have definitely caused DRESS, for after low dose re-exposure the patient promptly showed slightly eosinophilia and CRP ascent again. In the second case, the patient had edema, eosinophilia, and elevated liver enzymes under 200 mg clozapine in monotherapy, which implicates clozapine as a probable inductor of the DRESS. In our third case, liver enzymes elevation and skin exanthema, as well as CRP eleva-

tion, were described in the patient receiving clozapine and sertraline. Immunological reactions are much more often to be found with patients who are administered clozapine than in patients who receive sertraline, so we regard clozapine as a probable and sertraline a possible inductor. Alternatively, it could be possible that both drugs contributed to the development of the symptoms. In 2 of our 3 cases, clozapine levels were in the toxic range despite normal dosages: pharmacogenetic tests for eventual polymorphism of cytochrom P450 1A2 were not performed. In both cases, CRP was massively increased at the same time, and it is possible that release of cytokines during the immunological inflammatory process led to the rise in clozapine levels, as cytokines are known to inhibit clozapine metabolism via the inhibition of cytochrome 450 1 A2 [7]. Two out of the 3 patients were treated with

corticosteroids and all ceased taking clozapine. Under this therapy regime, the patients achieved a complete remission.

In general, unwanted drug effects as a cause of medical disorders often remain undetected. DRESS in particular appears to be difficult to recognize: since DRESS involves very different symptoms of various organ systems, it is possible that in clinical routine not all symptoms are noticed and not subsumed to this complex, and therefore DRESS remains unrecognized. However, since the disease is severe and the consequences can be dramatic, it is important to know about the possibility of DRESS due to drugs in order to intervene quickly, if so necessary.

DRESS must be recognized promptly and the causative drug withdrawn. It has been

reported that the earlier the drug is withdrawn, the better the prognosis [8].

DRESS is mostly seen and described in patients receiving rheumatologic or anticonvulsant drugs but very rarely in psychiatric hospitals, where clozapine is frequently used. It is the aim of this report to alert psychiatrists to this rare but severe adverse drug reaction of clozapine.

Conflict of Interest

S. Toto is a project manager of AMSP, has been a member of an advisory board for Otsuka and has received speaker's honoraria from Janssen Cilag, Lundbeck, Otsuka and Servier

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