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(CASE REPORT)

Sulfone syndrome due to sulfasalazine use in treatment of Rheumatoid Arthritis: A case report and a review of literature

Tunde Maiyaki Ibrahim [1, 2, *]

[1] *Medicine Department, Goulburn Valley Health, Graham Street, Shepparton.Vic 3630, Australia.*
[2] *Shepparton Rural Clinical School, the University of Melbourne, Department of Rural Health, 49 Graham Street. Shepparton, Vic 3630, Australi.*

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Abstract

Background: Sulfone syndrome has been reported in patients treated with *sulfur c*ontaining agents such as dapsone and carbamazepine for almost a century. But not much as being discuss about it in recent literature. I present a case of sulfone syndrome which occurred.

Clinical Case: I present the rare case of a 76-year-old female with rheumatoid arthritis who two weeks after starting sulfasalazine developed systemic symptoms of fever with chills and rigors, headache, and maculopapular skin rash. She had severe mixed picture deranged hepatic function (Hepatocellular and cholestatic picture) and pancytopenia. Microbiological investigations revealed no microbial etiology. The patient was treated with prednisolone and supportive therapy including discontinuation of the sulfasalazine. Her symptoms improved and resolved within 5 days. The pancytopenia resolved in a week and liver function test gradually improved and normalized by 90 days.

Conclusion: Although sulfone syndrome can resolve once the offending sulfur agent is discontinued it can cause severe morbidity and mortality. Therefore. I urge physician starting patients on sulfur containing agents such as sulfasalazine to always watch out for sulfone syndrome as a possible adverse reaction.

Keywords: *Adverse drug reaction*; Rheumatoid arthritis (RA); Sulfasalazine; Sulfone syndrome

1. Introduction

Sulfasalazine is an anti-inflammatory agent that as long been used in the treatment of several seropositive and seronegative arthropathies such as rheumatoid arthritis, axial spondyloarthropathy and psoriatic arthritis for many decades.[1-3] . Sulfasalazine composed of *sulphapyridine* and 5-aminosalacyclic acid moieties joined by an azo bond which is broken by bacteria azo reductases in the colon lumen releasing the dispensable toxic *sulphapyridine* which is absorbed and 5-ASA, that acts locally as anti- inflammatory.[4,5] The common adverse drug reactions (ADR) from sulfasalazine use include anorexia, headache, nausea, gastrointestinal upset, fever, arthralgias, dermatological disorders, hematological disorders, hepatitis, interstitial nephritis, carditis and azoospermia. Severe hepatitis including acute hepatic failure have also been reported[3, 6,7] Jobanputra et-al,[8] reported that 0.4% of patients with rheumatoid arthritis (RA) treated with sulfasalazine may experience severe hepatic toxicity. A combination of these ADS with hepatitis and systemic symptoms as the main feature have been observed in some users of sulfasalazine resulting in a clinical condition called sulfone syndrome and DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) a term mostly used in the American literature if dermatological reactions and eosinophilia are the main features. The sulfone and DRESS syndrome are idiosyncratic hypersensitivity reaction to the sulphapyridine component of sulfasalazine as in other

* Corresponding author: Tunde Maiyaki Ibrahim

sulfur containing agents.[9,10] Although these syndromes and hepatotoxicity due to sulfur containing agents may be rare, they can be very severe and results in fatality. Therefore, this case report is to remind clinicians about the existence of this potentially fatal syndrome first observed about a century ago so that they would regularly watch out for it by monitoring for systemic symptoms, derange liver functions and blood dyscrasias in patients on sulfasalazine.

2. Case Report

The patient was a 76-year-old woman with rheumatoid arthritis (RA), hypertension and dyslipidemia who presented with 6 days history of malaise and 3 days of headache, vomiting, fever, chills and rigors, and dark urine. Her symptoms started about 2 weeks after starting sulfasalazine 500mg BID. Other medications been used were evolucomab monthly injection for dyslipidemia, telmisartan and *lercanidipine* for hypertension, esomeprazole for gastroesophageal reflux disease and prednisolone for the RA. She had partial parathyroidectomy some years ago for primary hyperparathyroidism and drink only one standard alcohol drink daily. There were no other abdominal symptoms. Physical examination revealed fever with high body temperature of 38.6^{oC} but other vital signs were normal. *Systemic examination was essentially normal except for nonpruritic maculopapular rash on the truck and back. and mild deforming Poly arthropathy of the hands from the RA.* There was no jaundice or sign of hepatic failure. Urinalysis, blood cultures and CSF were normal with no evidence of urinary tract infection, septicemia or meningitis. However, there was a mixed picture deranged liver function test with very high transaminases and cholestatic enzymes. Full blood count revealed pancytopenia with reactive lymphocytes and mild rouleaux formation seen on the blood film. The details of the time course of LFT, FBE and CRP progression during her admission and follow-ups are shown in table 1 and figure 1. Viral Hepatitis serology for hepatitis,A,B,C and E was negative except for elevated IgG hepatitis A antibody suggesting previous hepatitis A infection or vaccination. Serology for EBV and CMV showed evidence of previous infections with elevated IgG anti EBV and CMV antibodies. Screening for autoimmune hepatitis showed negative extranuclear antigens, anti-liver,kidney and microsomal antibody, and anti- mitochondrial antibody. The ANA was mildly positive at 1:160 with none homogenous pattern,this can be seen in any inflammatory condition. Flavi viruses and leptospiral serology were also negative. Ultrasound and CT scan of her abdomen was essentially normal. She received empirical ceftriaxone and acyclovir for 48hrs for presumed meningitis on admission. These were stopped after the sterile CSF and negative blood cultures reports were received. She was subsequently diagnosed with sulfone syndrome due to sulfasalazine based on the consternation of symptoms of fever,chills and headache,amucopapular skin rash, hepatitis and pancytopenia. To manage this the sulfasalazine was discontinued and the dose of prednisolone was increased from 5mg to 15mg daily. She was monitor with regular biochemistry and hematology tests. After 48hrs of admission she stopped having fever and the skin rashes resolved. The LFT and FBE though fluctuated during her admission eventually improved significantly as the days goes bye and the patients was discharged 5 days after admission. Ninety days post discharged she was asymptomatic and the LFT was back to normal except for mildly elevated GGT (44 IU/l).

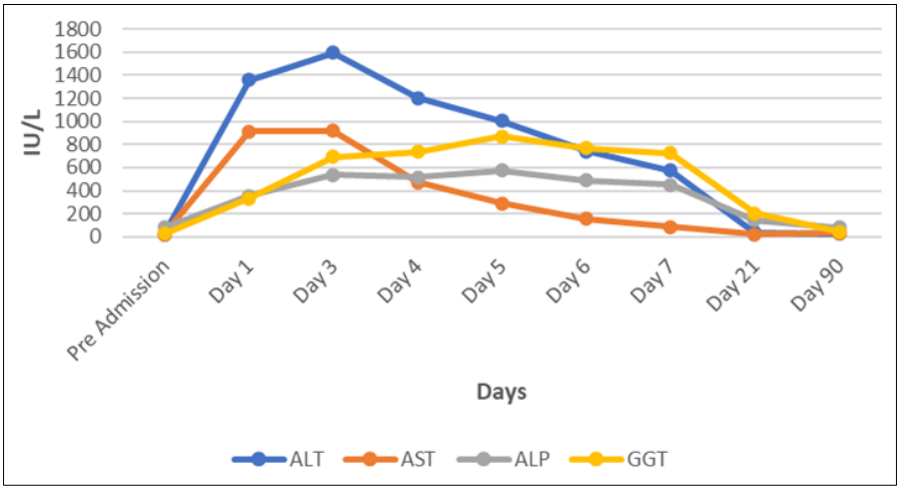

Figure 1 Time course of live enzymes

Table 1 The time course of abnormal liver function tests, C-reactive protein, and full blood count

Days after stopping Sulfasalazine									
Tests	**Pre-Sulfazalazine**	**Day 1**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 21**	**Day 90**
LFT									
Bilirubin mmol/l)	5	4	9	8	7	7	7	6	4
Albumin (mg/l)	40	32	51	49	60	57	59	66	66
Total Protein(md/dl)	67	58	28	26	31	30	33	40	40
Liver enzymes									
ALT (UI/L)	23	1359	1596	1206	1003	744	575	36	28
AST (IU/L)	21	914	917	471	288	158	87	24	35
GGT(IU/L)	25	333	694	736	869	769	726	204	44
ALP (IU/L)	83	353	536	514	573	487	453	144	83
FBE									
Hb (mg/l)	131	122	112	106	119	117	125	128	
WCC(x 10^9/l)	5.5	2.8	2.5	3.4	4.0	4.0	4.5	6.6	
Neutro(x 10^9/l)	2.7	1.5	1.1	1.3	2.3	1.7	1.6	5.0	
Lymph(x 10^9/l)	2.1	1	1	1.5	1.4	1.7	2.3	1.4	
Eosino(x 10^9/l)	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.0	
Platelets(x 10^9/l)	242	147	139	156	228	240	303	303	
CRP (mg/l)	4.0	118	73	48	30	18	11	4.0	

3. Discussion

Sulfasalazine is a drug with anti-inflammatory moiety the 5- Amino Salicylic Acid (5-ASA) and the sulphapyridine which is the dispensable and transport constituent.[5] The Sulphapyridine moiety is very toxic and is responsible for most of the ADR reported in sulfasalazine use. Reported sulfasalazine ADR include gastrointestinal upsets, mucocutaneous disorders, Blood dyscrasias, pancreatitis, carditis, deranged liver and renal functions that are usually self-limiting and not life threatening.[6,8,11]. More serious systemic adverse reactions due to the sulphapyridine component of sulfasalazine includes hepatitis, interstitial nephritis, DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and sulfone syndromes. These reactions have been reported in various *sulfur* containing medications such as dapsone, sulfasalazine and carbamazepine.[12-15] Patients on sulfasalazine were 3 times more likely to withdraw from treatment than placebo (22% vs 8%) because of ADR. The most frequent side effects responsible for discontinuation of sulfasalazine include gastrointestinal symptoms (10%), mucocutaneous reactions (7%), and hematological abnormalities (2%).[6,11,12] Sulfone syndrome is a rare serious toxicity due to *sulfur* containing agents characterized by systemic symptoms such as malaise, fever, chills and rigors, headache, skin rashes, hepatitis and hematological abnormalities mostly *hemolytic* anemia.[13] These features are very similar to those seen in DRESS syndrome a term mostly used in USA.[12]. The difference is that DRESS syndrome as the named implies is mostly characterized by exanthem and eosinophilia while sulfone syndrome is characterized mainly by hepatitis and systemic symptoms with or without exanthem and eosinophilia. Severe hepatitis is a cardinal feature of sulfone syndrome and have resulted in acute hepatic failure and even death in some cases. The hepatic dysfunction may be of hepatocellular, cholestatic or mixed picture as seen in the reported case. There was no obvious *hemolysis* in the reported case, but she developed transient pancytopenia and had reactive atypical lymphocytes which has been observed in other reported cases of sulfone syndrome. Sulfone syndrome has been described by various names since its recognition nearly a century *ago*. This include dapsone hypersensitivity syndrome first described by Lowe and Smith[16], in 1949 when they noted exfoliative dermatitis among 2% of patients with leprosy treated with dapsone. After this the clinical conditions with features like that seen in sulfone syndrome was described as a "Mononucleosis like syndrome" characterized by exfoliative dermatitis, jaundice, hepato-splenomegaly, lymphadenopathy, and a predominance of peripheral blood lymphocytosis in patients with leprosy and tuberculosis

treated with dapsone. [17]. Lastly is DRESS syndrome which is almost indistinguishable from the sulfone syndrome as they both shear the same clinical and pathological features. Except that as the name implies DRESS syndrome is mainly characterized by dermatological disorders and eosinophilia. Drug induced organ damage such as hepatotoxicity can be a result of toxicity from the drug or it's metabolites on hepatocytes or by activating the immune system. Hepatitis from sulfasalazine and most other sulphapyridine containing agent is believed to be due to an idiosyncratic delayed type hypersensitivity reaction. The dosage of the medications appears to play a very minimal if any role in the likelihood of developing the syndrome. These affects most organs in the body not just the liver and is mainly due to eosinophil infiltration of the organs.[14,18] Therefore, the sulfone syndrome is most likely due to idiosyncratic hypersensitivity reaction rather than a toxic reaction. In contrary MacGilchrist and Hunter,[19] reported a case of sulfasalazine induced hepatic toxicity with no evidence of hypersensitivity. The reported case might be like that reported by MacGilchrist and Hunter,[19] where eosinophilic hypersensitivity is not to blame. As there was no peripheral blood eosinophilia in the reported case, and it is not possible to say if there was hepatic eosinophil infiltration as no liver biopsy was indicated nor performed in this case. By reviewing 21 reported cases Mohle-Boetani et -al [10], proposed what might be referred to as the diagnostic criteria for sulfone syndrome which include that cases will occur within two months of the patients starting sulphur containing agents (in their case dapsone), presence of fever, a rash, evidence of hepatic injury (hepatocellular and cholestatic injury, hepatomegaly, jaundice, or hyperbilirubinemia), atypical lymphocytosis and haemolytic anaemia. The reported case had most of these features which included: onset of illness within two weeks of initiating sulfasalazine treatment, fever, headache, vomiting, skin rash, atypical lymphocytosis, anemia, and elevated aminotransferases and cholestatic enzymes levels. However, despite severe hepatocellular and cholestatic damage there was no jaundice nor hepato-splenomegaly. This case also has most features seen in DRESS syndrome but the absence of peripheral blood eosinophilia which is a cardinal feature of DRESS syndrome made me think the diagnosis in this case was sulfone syndrome rather than DRESS syndrome. Sulfone syndrome is often misdiagnosed as a viral infection just as it was initially suspected in this case but all virology testing as in this reported case will be negative. Sulfone syndrome can be difficult to differentiate from DRESS syndrome as both are characterized by exanthem, pyrexia, elevated white blood cells with eosinophilia or abnormal lymphocytes, swollen lymph nodes, and kidney or hepatic disorders. Reading through the literature in my opinion sulfone and DRESS syndromes are likely the same clinical entity with a lot in common but with few differences. Mainly that DRESS syndrome almost always as the name implies will have exanthem and peripheral blood eosinophilia which are not always present in sulfone syndrome. Therefore, the nomenclature depends on which of the clinical features predominate. While hepatitis and systemic symptoms predominate in sulfone syndrome, exanthem and eosinophilia are the cardinal features of DRESS syndrome. [10,12,14]Most cases of acute hepatitis due to sulfasalazine including those with sulfone syndrome resolve rapidly once the *sulfur* containing agent is withdrawn usually within 2 to 4 weeks unless cholestasis is severe [7]. The management of sulfone syndrome and sulfasalazine induced hepatitis involves mainly the cessation of the medication and use of steroid. [14,17] But as some patients who develop this syndrome is already on steroid it appears not to prevent it development. The index case like that reported by Barnard, Scharf & Dagher [20] was on prednisolone before starting the sulfasalazine and subsequently developed the sulfone syndrome. But she responded excellently to increase dose of prednisolone.

4. Conclusion

I conclude that clinician who prescribe *sulfur* containing agents such as sulfasalazine should watch out for systemic symptoms and hepatotoxicity in association with, skin rash, pancytopenia and reactive lymphocytes in peripheral blood which may suggest sulfone syndrome. This can occur within 2 months of starting *sulfur* containing agent and respond well to discontinuation of the offending agent.

Compliance with ethical standards

Acknowledgments

I thank the staff in Health information department for making it easy for me to access the patient's record through their proper coding and entry.

Statement of informed consent

As per the rules in our organization implied informed consent was obtained from the patient included in this study as no name or the picture was use.

References

[1] McConkey B, Amos R S, Durham S, Forster P J G, Hubbal S, Walsh L. Sulphasalazine in rheumatoid arthritis. Br Med J.1980: 442-444

[2] Suarez-Almazor ME, Belseck E, Shea B, Tugwell P, Wells GA. Sulfasalazine for treating rheumatoid arthritis.Cochrane Database of Systematic Reviews 1998, Issue 2. Art. No.: CD000958.DOI: 10.1002/14651858.CD000958.

[3] Greg L Plosker 1, Katherine F. Sulfasalazine: a review of its use in the management of rheumatoid arthritis. Drugs. 2005;65(13):1825-49. doi: 10.2165/00003495-200565130-00008. Croom Affiliations expand.

[4] Rains C P, Noble S, Faulds D. Sulfasalazine. A review of its pharmacological properties and therapeutic efficacy in the treatment of rheumatoid arthritis. Review Drugs. 1995 Jul;50(1):137-56. doi: 10.2165/00003495-199550010-00009.

[5] Khan A K, Piris J, Truelove S C. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet 1977;2:892–895

[6] Jayachandran M, Koshy V, David R, Santhakumari V, Padmanabhan D S, Surendran S, Arun Tiwari A, Mithun C B, Singh S K , Suman S K, Yadav P, Singhal A, Nair A S, Marwaha V, PalattyInt P L. Adverse reaction profile of sulfasalazine and its persistence in chronic therapy of rheumatoid arthritis and spondyloarthritis: J Clin Pharmacol Ther. 2022 Aug;60(8):327-335. doi: 10.5414/CP204120. A multicentric observational study. PMID: 35713159 DOI: 10.5414/CP204120.

[7] LiverTox: Clinical and Research Information on Drug Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Sulfasalazine. [Updated 2017 Sep 25].Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

[8] Jobanputra P, Amarasena R, Maggs F, Homer D, Bowman S, Rankin E, Filer A,Raza K,Jubb R. Hepatotoxicity associated with sulfasalazine in inflammatory arthritis: A case series from a local surveillance of serious adverse events. BMC Musculoskeletal Disorders 2008; 9:48:1-7 doi:10.1186/1471-2474-9-48

[9] Millikan LE, Harrell ER: Drug reactions to the sulfones. Arch Dermatol 1970;102:220-224

[10] Mohle-Boetani J, Akula SK, Holodniy M, Katzenstein D, Garcia G: The sulfone syndrome in a patient receiving dapsone prophylaxis for Pneumocystis carinii pneumonia. West J Med 1992 Mar; 156:303-306

[11] Ransford R A J, Langman M J S. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. Gut 2002;51:536–539

[12] Millican LE, Harrell ER: Drug reactions to the sulfones. Arch Dermatol 1970, 102:220-4.

[13] Johnson DA, Cattau EL, Kuritsky JN, Zimmerman HJ: Liver involvement in the sulfone syndrome. Arch Intern Med 1986, 146:875-77.

[14] Navarro VJ, Senior JR: Drug-related hepatotoxicity. N Eng J Med.200, 354:731-9.

[15] Edith Arce , Rodrigo Quera , Lilian Flores, Rodrigo Blamey.[DRESS syndrome induced by sulfasalazine. Report of one case].Rev Med Chil . 2020 Aug;148(8):1213-1218. doi: 10.4067/S0034-98872020000801213.

[16] Lowe J, Smith M. The chemotherapy of leprosy in Nigeria; with an appendix on glandular fever and exfoliative dermatitis precipitated by sulfones. Int J Lepr. 1949;17:181–195.

[17] Sahm J, de Groot K, Schreiber J. Sulfasalazine-induced mononucleosis-like-illness and *hemolysis*. Scand J Rheumatol.2021;50(1):83-84. doi: 10.1080/03009742.2020.1747533. Epub 2020 May 29. Affiliations expand.PMID:32468961 DOI: 10.1080/03009742.2020.1747533

[18] Tas S, Simonart T: Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. Dermatology 2003, 206:353-6.

[19] MacGilchrist AJ, Hunter JA: Sulphasalazine hepatotoxicity: lack of a hypersensitivity response. Ann Rheum Dis 1986, 45:967-8.

[20] G F Barnard 1, M J Scharf, R K Dagher.Sulfone syndrome in a patient receiving steroids for pemphigus.Am J Gastroenterol. 1994 ;89(11):2057-9.