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Case Report Open Access

Agranulocytosis during Tuberculosis Therapy - Cautious Use Of Allopurinol

Sheng Hsiang Ma[1] and Chun Hsing Liao*[2]

[1]Department of medicine, National Yang-Ming University, Taiwan

[2]Department of Internal Medicine, Far Eastern Memorial Hospital, Taiwan

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***Corresponding author:** Chun Hsing Liao, Department of Internal Medicine, Section of Infectious Disease, Far Eastern Memorial Hospital, 21 Nan-Ya South Road, Section 2, Dist. Banquiao, New Taipei City, Taiwan

Case Report

A 61-year-old man had a past history of type II diabetes mellitus, stage four chronic kidney disease, coronary artery disease and congestive heart failure under medical treatment. During September 2012, he was admitted due to general weakness, and was later diagnosed with pulmonary and peritoneal tuberculosis. Rifampin, isoniazid, ethambutol and pyrazinamide were prescribed as standard treatment. The patient's serum creatinine was 3.6mg/dL with hyperuricemia (9.8mg/dL). Considering his hyperuricemia and history of gout, allopurinol 100mg/day was also initiated.

However, fever with chills developed two weeks after discharge. He visited emergency department on October 13th. Examination revealed fever (38.8°C), tachycardia (129/min), tachypnea (20/min), oral ulcer, icteric sclera, bilateral lower legs edema and diffuse morbilliform skin rash. Anemia (hemoglobin 4.7mg/dL), thrombocytopenia (100000/μL), leukopenia (1800/μL), and neutropenia (5%) were found without eosinophilia (0%). Laboratory data revealed elevated creatinine (4.4mg/dL), LDH (330IU/L) and total bilirubin level (2.6mg/dL), while liver enzyme levels were within normal range. Adverse drug reaction was considered and all prior medications were discontinued. Cefepime and levofloxacin were prescribed for his neutropenic fever, accompanied with empirical fluconazole. Besides, filagrastim was also initiated. A bone marrow biopsy revealed normal cellularity and no decrease of precursor cells. On October 18th, leukopenia (1900/μL) and agranulocytosis (0.0%) were found, with persistent fever and multiple organ dysfunctions. One set of blood culture showed yeast growth, and fluconazole was shifted to micafungin. On October 23 rd, drop of blood pressure, dyspnea and progressive drowsiness were noted. The patient and his family refused further intervention and the patient expired this evening due to Candida tropicalis fungemia with septic shock after agranulocytosis.

Agranulocytosis, defined as neutrophil count under 0.5x109/L, is mostly induced by drugs [1,2]. Causative agent in this patient is difficult to be determined, because both anti-tuberculosis drugs and allopurinol had been reported (Table 1) [3]. We suggested allopurinol be the culprit of agranulocytosis in this case. First, previous research showed that allopurinol use within one week carried a relative risk of 6,7 to development of agranulocytosis compared to no use, but anti-tuberculosis agents had no similar analysis [2]. Second, the dose of allopurinol was not titrated slowly according to his renal function, increasing the possibility of allopurinol hypersensitivity [4]. Third, his liver enzyme levels were not elevated, which was the most common adverse effect of anti-tuberculosis drugs.

Table 1: Summary of agranulocytosis caused by allopurinol or anti-tuberculosis agents.

Title, author, publication year	Age	Sex	Drugs	Culprits	WBC	Neut(%)	Outcome
Allopurinol and agranulocytosis, Wilkinson, 1977	50	F	A	A	NA	0	dead
Aplastic agranulocytosis after allopurinol therapy, Greenberg, 1972	62	F	A	A	500	NA	dead
Agranulocytosis: an adverse effect of allopurinol treatment, Elisa, 2011	90	M	A	A	300	10	alive
Agranulocytosis during Isoniazid therapy, Varadi, 1953	20	M	H/P/S	H	4900	1	alive
Agraulocytosis caused by isonicotinic acid acid hydrazide, Adar, 1953	14	F	H/P	H	1600	0	alive
Agranulocytic reaction in a woman with pulmonary tuberculosis, Spesivtsev, 1968	18	F	H/S/ etoxyd	H/S/ etoxyd	3300	1	alive
Agrnulocytosis following isoniazid- a case report, Sharma, 1979	23	M	H	H	2300	10	alive

2 cases of neutropenia during treatment of pulmonary tuberculosis, Weslaew, 1969	21	F	H/S/P/E	H/S/P/E	4000	2	alive
Acute agranulocytosis in a pregnant woman treated for pulmonary tuberculosis, Livandovskii, 1969	23	F	H/S/ etoxyd	H/S/ etoxyd	700	0	alive
Anaphylatic bone marrow crisis following isoniazid therapy, Horvath, 1970	51	F	H	H	2400	0·5	alive
Agranulocytosis due to INH toxicity, Ahuja, 1970	50	F	H/S	H	3600	0	alive
Agranulocytosis following isoniazid, Mechrotra, 1973	37	M	H/S/	H	2000	6	alive
Agranulocytosis due to anti-tuberculosis drugs including Isoniazid and Rifampicin, Shishido, 2003							
Case1	51	F	H/R/E/ Z/A	R	1300	1	alive
Case2	66	M	H/R/E	R	2300	2	alive
Case3	60	F	H/R/E/ Z/A	Z?	900	1	alive
Case4	60	M	H/R/S	H/R/S	800	0	dead
A case of agrnulocytosis caused by rifampicin during treatment of tuberculous lymphadenitis in a chronic renal failure patient, Squiyama, 2012	52	F	H/R/E/Z	R	2100	5	alive
Our case	61	M	H/R/E/ Z/A	A	1900	0	dead

A: Allopurinol; H: Isoniazid; R: Rifampin, Z: Pyrazinamide, S: Streptomycin; E: Ethambutol, P: Para-aminosalitilic acid; NA: not available

Allopurinol induced agranulocytosis was reported mainly among patients with leukemia receiving chemotherapy [1,3,4]. On the contrary, there were fewer reports of agranulocytosis caused by allopurinol among patients receiving tuberculosis treatment. In the report of Shishido, they reported four cases of agranulocytosis and attributed the causes to anti-tuberculosis medications [2]. However, two out of the four patients also used allopurinol, for which allopurinol related agranulocytosis cannot be completely ruled out. As allopurinol can lead to lethal hypersensitivity and agranulocytosis, its use should be assessed carefully. During treatment for tuberculosis, pyrazinamide can cause and aggravate hyperuricemia, but mostly asymptomatic. As a result, prophylactic use of allopurinol is not suggested. Once needed, genetic testing (HLA-B5801) before usage should be considered [5].

Patients with agranulocytosis are at risk of severe infection even aggressively treated. Discontinuation of the possible medication is the single most important intervention, but it is sometimes difficult to identify the causative agent. G-CSF can be used, but not all studies indicated its benefits. Broad spectrum antibacterial agents should be initiated for patients with sepsis, but the role of empirical antifungal agent is controversial. For this patient, we used strong antimicrobial agents empirically, while he still developed breakthrough candidemia and died. In conclusion, prophylactic use of allopurinol for hyperuricemia among patients receiving tuberculosis treatment should be avoided.

Contributors

SH and CL reviewed the case and literature together. SH prepared the manuscript. All authors contributed to drafting the manuscript and approved the final version. CL Liao had full access to all the data, and had final responsibility for the decision to submit for publication.

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