

# Agranulocytosis Induced by Ethambutol in a Patient with Pulmonary Tuberculosis

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We report a case of agranulocytosis caused by ethambutol in a 79-year-old man with pulmonary tuberculosis. He was referred for fever and skin rash developed on 21th day after antituberculosis drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) intake. Complete blood count at the time of diagnosis of pulmonary tuberculosis was normal. On the seventh admission day, agranulocytosis was developed with absolute neutrophil count of 70/ $\mu$ L. We discontinued all antituberculosis drugs, and then treated with granulocyte colony-stimulating factor. Three days later, the number of white blood cell returned to normal. We administered isoniazid, pyrazinamide, and ethambutol in order with an interval. However, fever and skin rash developed again when adding ethambutol, so we discontinued ethambutol. After these symptoms disappeared, we added rifampicin and ethambutol in order with an interval. However after administering ethambutol, neutropenia developed, so we discontinued ethambutol again. He was cured with isoniazid, rifampicin, and pyrazinamide for 9 months.

**Keywords:** Agranulocytosis; Ethambutol; Tuberculosis, Pulmonary

## Introduction

Antituberculosis drugs may induce hematologic side effects such as thrombocytopenia and neutropenia, but agranulocytosis has rarely been reported. We describe a patient who developed agranulocytosis induced by ethambutol.

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## Case Report

A 79-year-old man was referred to our hospital for fever and skin rash showed no further improvement with antipyretic drug and fluid therapy on 3 weeks after taking antituberculosis drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) at other hospital. Three weeks ago, he was diagnosed with pulmonary tuberculosis by positive acid-fast bacilli. Complete blood count (CBC) at the time of diagnosis of pulmonary tuberculosis was white blood cell (WBC) of  $6.70 \times 10^3/\mu\text{L}$ , absolute neutrophil count (ANC) of  $3.37 \times 10^3/\mu\text{L}$ , hemoglobin of 11.9 g/dL, and platelet of  $323 \times 10^3/\mu\text{L}$ . He denied other medical disease except the known pulmonary tuberculosis.

On the seventh admission day, agranulocytosis was developed with ANC of 70/ $\mu\text{L}$ . The patient had WBC of  $1.63 \times 10^3/\mu\text{L}$ , hemoglobin of 12.2 g/dL, and platelet of  $310 \times 10^3/\mu\text{L}$ . We stopped all antituberculosis drugs, and then treated with granulocyte colony-stimulating factor, subcutaneous dose of 300  $\mu\text{g}$  of biosimilar filgrastim. Three days later, the number of WBC was  $8.46 \times 10^3/\mu\text{L}$  and the number of ANC was  $3.15 \times 10^3/\mu\text{L}$  (Figure 1). And then he was administered only isoniazid again for 3 days. Since there was no adverse effects, we added pyrazinamide and ethambutol, respectively with an interval.

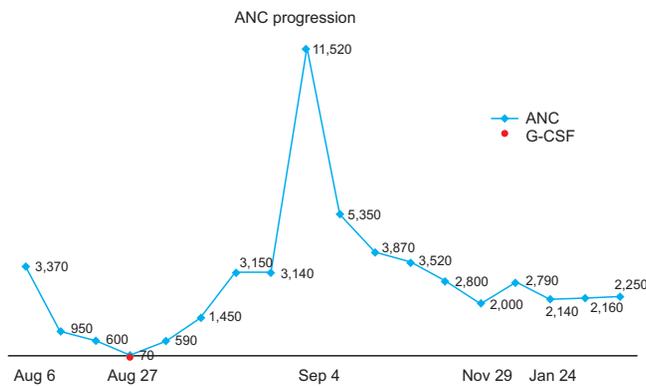
However, we stopped ethambutol due to fever and skin rash arised after adding ethambutol. There were no adverse effects of isoniazid and pyrazinamide for several days, so we added

rifampicin and added ethambutol again with an interval. However, due to relapse of neutropenia (ANC of  $1.43 \times 10^3/\mu\text{L}$ ) in the sixth day after administrating ethambutol, we stopped ethambutol. And we continued isoniazid, rifampicin, and pyrazinamide for 9 months. He was cured without any other hematologic disorders.

Judging from the clinical course, we could conclude that ethambutol had caused agranulocytosis (Table 1).

## Discussion

Antituberculosis drugs have been shown to produce adverse effects from insignificance to life-threatening. In an immunocompetent patient, neutropenia is rare adverse effects of antituberculosis therapy. However, neutropenia combined with sepsis could lead to life-threatening. Umeki<sup>1</sup> reported that the incidence rate of neutropenia and agranulocytosis due to antituberculosis drugs were observed in 10.9% and 3.96%, respectively. Shishido et al.<sup>2</sup> reported that the incidence rate of



**Figure 1.** Patient's absolute neutrophil count (ANC) progression from the onset of antituberculosis therapy. G-CSF, granulocyte colony-stimulating factor.

**Table 1.** Antituberculosis medications and alterations in the hematologic indices

Medication		WBC ( $\times 10^3/\mu\text{L}$ )	Neutrophil (%)	ANC ( $\times 10^3/\mu\text{L}$ )	Eosinophil (%)	Hemoglobin (g/dL)	Platelet ( $\times 10^3/\mu\text{L}$ )	
HREZ (Aug 3)	Aug 6	6.70	50.3	3.37	4.6	11.9	323	
	Aug 22	3.44	27.7	0.95	9.4	12.7	299	
	Aug 24	2.82	21.3	0.60	9.5	11.6	311	
Antituberculosis medication stopped (Aug 27)	Aug 27	1.63	4.1	0.07	14.0	12.2	310	
	Aug 28	2.43	24.1	0.59	13.2	12.5	321	
	Aug 29	4.64	31.2	1.45	6.6	11.6	280	
	Aug 30	8.46	37.2	3.15	9.8	12.7	296	
	H (Aug 31)	Aug 31	8.20	38.4	3.14	8.0	12.1	291
	HZ (Sep 3) HZE (Sep 4)	Sep 4	13.99	82.3	11.52	2.6	14.3	295
E stopped (Sep 6)	Sep 6	9.75	54.9	5.35	6.0	11.8	243	
	Sep 8	7.17	53.9	3.87	9.2	12.0	243	
HZR (Sep 10) HZRE (Sep 11)	Sep 12	7.07	49.7	3.52	8.7	12.0	275	
E stopped (Sep 17) HZR (Sep 17)	Sep 17	5.21	27.5	1.43	31.5	12.1	310	
	Oct 10	5.78	48.4	2.8	3.5	13.1	245	
	Nov 29	4.54	44.1	2.0	3.2	13.3	221	
	Dec 27	5.57	50.2	2.79	2.3	13.6	170	
	Jan 24	4.71	45.4	2.14	1.9	13.7	202	
	Feb 28	5.12	42.1	2.16	2.1	13.8	205	
	Mar 28	4.69	47.9	2.25	1.6	13.9	202	

WBC: white blood cell; ANC: absolute neutrophil count; H: isonicotinic acid hydrazide; R: rifampicin; E: ethambutol; Z: pyrazinamide.

agranulocytosis due to antituberculosis drugs was estimated at 0.06%. Therefore, it is important to detect neutropenia earlier and treat it in a patient taking antituberculosis drugs.

The causes of agranulocytosis mentioned above<sup>1,2</sup> were not ethambutol, but rifampicin and isoniazid. The important adverse effects of ethambutol are visual disturbance due to retrobulbar neuritis and toxicities to peripheral nerves<sup>3,4</sup>. There is no well-documented report of agranulocytosis induced by ethambutol. Though Wong and Yew<sup>5</sup> suggested an association of neutropenia (ANC of  $1.4 \times 10^3/\mu\text{L}$ ) with ethambutol, but it was not agranulocytosis, but mild neutropenia.

Our case is the first report of agranulocytosis induced by ethambutol. According to the previous reports<sup>1,2,6,7</sup>, neutropenia can be developed in a patient who is treated with antituberculosis drugs during a few months after starting administration. In administering antituberculosis drugs including ethambutol, as in our case, we should regularly make a close monitoring of the CBC to avoid serious events.

### Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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