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Abstract

Amiodarone is an important antiarrhythmic drug used worldwide. Although there have been reports of neutropenia or agranulocytosis induced by antiarrhythmic agents, the frequency of amiodarone-induced agranulocytosis is quite rare. Here, we report a case of a Japanese male who presented with agranulocytosis that was considered to be induced by the administration of amiodarone.

Introduction

Amiodarone is a drug mainly used in the treatment of cardiac arrhythmias. Amiodarone is categorized as a class III agent according to the Vaughan-Williams classification; it functions by inhibiting the potassium channels of myocardial cell membranes, resulting in a prolongation of the duration of action potential and effective refractory period[1)2)]. While amiodarone is widely used in the treatment of fatal supraventricular and ventricular arrhythmias, the frequency of adverse effects associated with amiodarone therapy seems to be relatively high; some of these include severe interstitial pneumonia, thyroid function abnormalities and liver dysfunction[3)]. Extensive care should therefore be taken during amiodarone administration. Although neutropenia or agranulocytosis induced by antiarrhythmic agents has also been reported, the frequency of amiodarone-induced agranulocytosis is quite rare. Here, we present a case of a Japanese male who presented with agranulocytosis that was considered to be induced by amiodarone administration.

Case Report

The clinical progress of a 60-year-old Japanese male diagnosed with atrial fibrillation and tachycardia was followed by a cardiologist. The patient was administered warfarin and bisoprolol, but his heart rate could not be properly controlled. Amiodarone administration was then begun in April, 2012. No abnormal finding was observed in his blood examinations at that point. About a week after amiodarone administration was initiated, he experienced fever and consulted a physician. He was treated with clarithromycin and a multi-ingredient cold medicine, but the fever did not improve. He consulted his physician again and this time severe neutropenia was observed upon blood examination. He was then referred to our department, and subsequently admitted for further examination on day 13 after amiodarone therapy had begun. He did not have any past history of adverse effects with these drugs.

On admission, his body temperature was 39.3°C. His heart rate was 73 per minute, but not regular. His throat was slightly reddish, but no other abnormal findings were observed.

Laboratory data on admission showed that WBC was 0.6 x 10^9/L with a neutrophil count of only 7%. Neither anemia nor thrombocytopenia was observed. Biochemical data showed liver dysfunction with slight jaundice, including AST 180

IU/L (normal range, 0-30 IU/L), ALT 92 IU/L (0-30 IU/L), ALP 560 IU/L (104-338 IU/L), γ-GTP 449 IU/L (0-50 IU/L), total bilirubin (T-Bil) 2.6 mg/dL (0.2-1.2 mg/dL), and direct bilirubin (D-Bil) 1.4 mg/dL (0.0-0.3 mg/dL). C reactive protein (CRP) was also high (19.72 mg/dL). The results of viral examination, including HBs-antigen, HCV antibody, and anti-Parvovirus B-19 antibody were all negative. Determination of antibodies against cytomegalovirus and Epstein-Barr virus indicated that he had previously been infected, but there was no evidence of viral reactivation. No abnormal values for thyroid hormones were observed (Table 1).

Bone marrow aspiration showed a hypocellular marrow without any evidence of dysplasia. Granulocyte numbers were especially reduced, but some immature granulocytes were observed (Figure 1). G-band analysis showed a normal karyotype.

Computed tomography (CT) scan showed mild cervical lymphadenopathy, but there was no other significant finding indicating infection or interstitial pneumonia.

Because there was no other obvious reason for the severe neutropenia, amiodarone therapy was stopped and instead granulocyte-colony stimulating factor (G-CSF) therapy was begun. Clarithromycin was changed to cefepim, and micafungin therapy was also started. His neutrophil count gradually increased, and the fever also decreased. Liver dysfunction also improved. The neutrophil count increased to 2.7×10^9

/L on day 7, and as such G-CSF therapy was stopped. He did not experience neutropenia and fever again, and was discharged on day 17 (Figure 2).

Discussion

Severe selective neutropenia is typically described as agranulocytosis. Agranulocytosis is a rare but sometimes life-threating condition due to the increased risk of severe infections. Agranulocytosis has been reported to be caused by several factors, and drug-induced agranulocytosis is known to be one of the most important clinical problems commonly observed. Drug-induced agranulocytosis is sometimes caused by drugs, of which some common examples include antithyroid or antipsychotic drugs[4)5)].

Although the mechanisms for the agranulocytosis have not been well elucidated, some speculations have been reported. One suggestion is that the drug or its metabolites are toxic to granulocyte precursor cells, and the other is that the drug induces immunological reactions to granulocytes by functioning as a hapten[6)]. The former takes several weeks to develop agranulocytosis, whereas the latter can cause agranulocytosis in only one week. Because the present case showed high fever only one week after the initial administration of amiodarone, we speculated that some immunological mechanisms should be considered.

Treatment of agranulocytosis involves the discontinuation of the suspicious drugs, with a subsequent observed improvement in neutrophil count within one to two weeks. Bone marrow aspiration findings may be an indicator for the time taken for neutrophil counts to improve; the presence of myelocytes or more immature cells within 7 days implies a rapid improvement, while the absence of these cells within 14 days implies a difficulty in improvement[5]. In the present case, some precursor granulocytes were observed in the bone marrow, and these cells might have contributed to the rapid improvement from the agranulocytosis[7].

In the past, the prognostic outlook for agranulocytosis was poor but this has improved in recent years due to advancement in treatment options. Antimicrobial drugs and G-CSF have been reported to be important in the treatment of agranulocytosis[5] ; and in the present case the early initiation of G-CSF administration might have contributed to the rapid improvement from the agranulocytosis.

In this report, amiodarone was considered to be the cause of the agranulocytosis considering the clinical course, although we did not test for the presence of anti-granulocyte antibodies. Agranulocytosis associated with high fever occurred soon after the initiation of amiodarone therapy, whereas rapid improvement was observed soon after the discontinuation of amiodarone therapy. Agranulocytosis

was confirmed to be present after clarithromycin administration hence it is highly unlikely that clarithromycin caused the agranulocytosis as the patient certainly experienced the high fever before the start of clarithromycin therapy.

Antiarrhythmic agents have been reported to cause agranulocytosis[4)5)] , but the real clinical frequency has not been well documented. In particular, the frequency of agranulocytosis during amiodarone therapy is not clear; there has been only one report where agranulocytosis was considered to be caused by amiodarone in a patient with chronic lymphocytic leukemia[8)].

In conclusion, we herein report a case of amiodarone-induced agranulocytosis. Although the occurrence of drug-induced agranulocytosis might not be frequent, it is important to keep in mind that when agranulocytosis occurs after the addition or initiation of therapy with new agents, the suspicious drug should be discontinued immediately. To achieve a good clinical course, it will be important to begin therapy with G-CSF and antimicrobial agents early.

Conclusion

We presented the very rare case who presented with agranulocytosis that was considered to be induced by the administration of amiodarone. The frequency of agranulocytosis by amiodarone seems to be very rare, but when starting to take

amiodarone, we should be observe to general condition of patients.

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Figure legends

Figure 1.

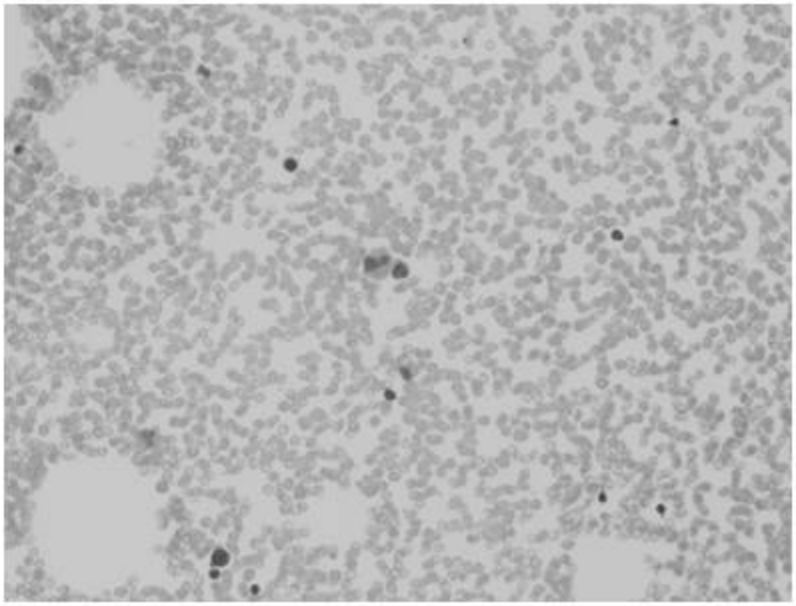
The smear finding of the bone marrow aspirate. Hypocellular marrow without any evidence of dysplasia was observed. Granulocyte numbers were severely reduced, but some immature granulocytes were observed.

Figure 2.

Clinical course of the present case. CAM: clarithromycin, G-CSF: granulocyte colony-stimulating factor, CFPM: cefepim, MCFG: micafungin.

Table I. Laboratory Findings at Admission

WBC	600	/μl	TP	7.0	g/dl	TSH	0.44	μIU/ml
Neut	7.0	%	Alb	3.6	g/dl	free T3	1.62	pg/ml
Lym	78.0	%	T-bil	2.6	mg/dl	freeT4	1.57	ng/dl
Mono	15.0	%	D-bil	1.4	mg/dl	RF	10	IU/ml
Eos	0	%	ALP	560	IU/l	ANA	<40	times
Baso	0	%	AST	180	IU/l	Fe	37	mg/dl
RBC	378×10^4	/μl	ALT	92	IU/l	TIBC	218	mg/dl
Hb	12.0	g/dl	LDH	216	IU/l	Ferritin	419	ng/ml
Ht	36.0	%	γ-GTP	449	IU/l	Haptoglobin	176	mg/dl
MCV	96.4	fl	BUN	32.1	mg/dl			
MCH	32.1	pg	Cre	1.00	mg/dl	HBsAg	0.00	IU/ml
MCHC	33.3	%	Na	145	mEq/l	HBsAb	136	mIU/ml
Plt	23.4×10^4	/μl	K	4.4	mEq/l	HCV-Ab	0.05	C.O.I
			Cl	107	mEq/l	EBV-VCA IgG		(+)
PT-INR	1.31		Ca	8.7	mg/dl	EBV-VCA IgM		(–)
APTT	36	sec	CRP	19.72	mg/dl	EBV-EBNA		(+)
Fib	607	mg/dl				CMV-IgG		(+)
D-dimer	3.7	μg/dl				CMV-IgM		(–)
						B19V		(–)



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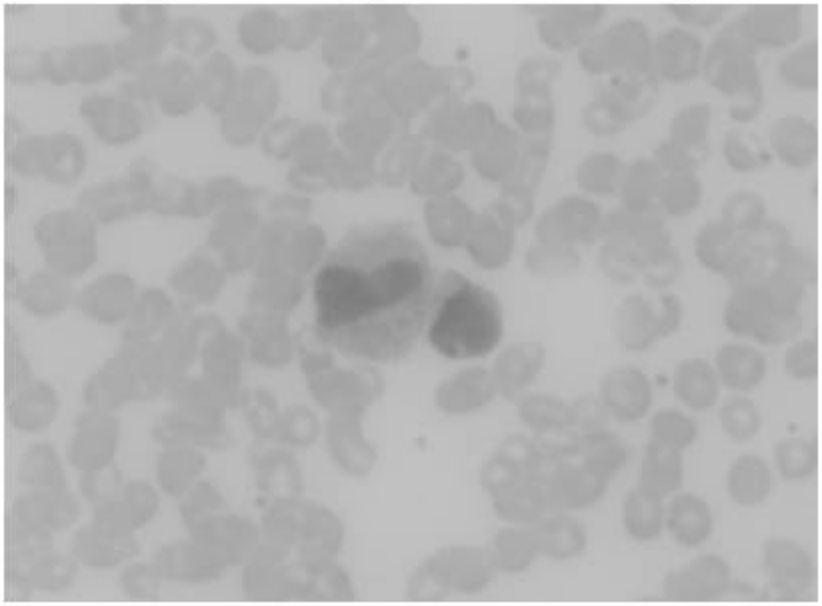

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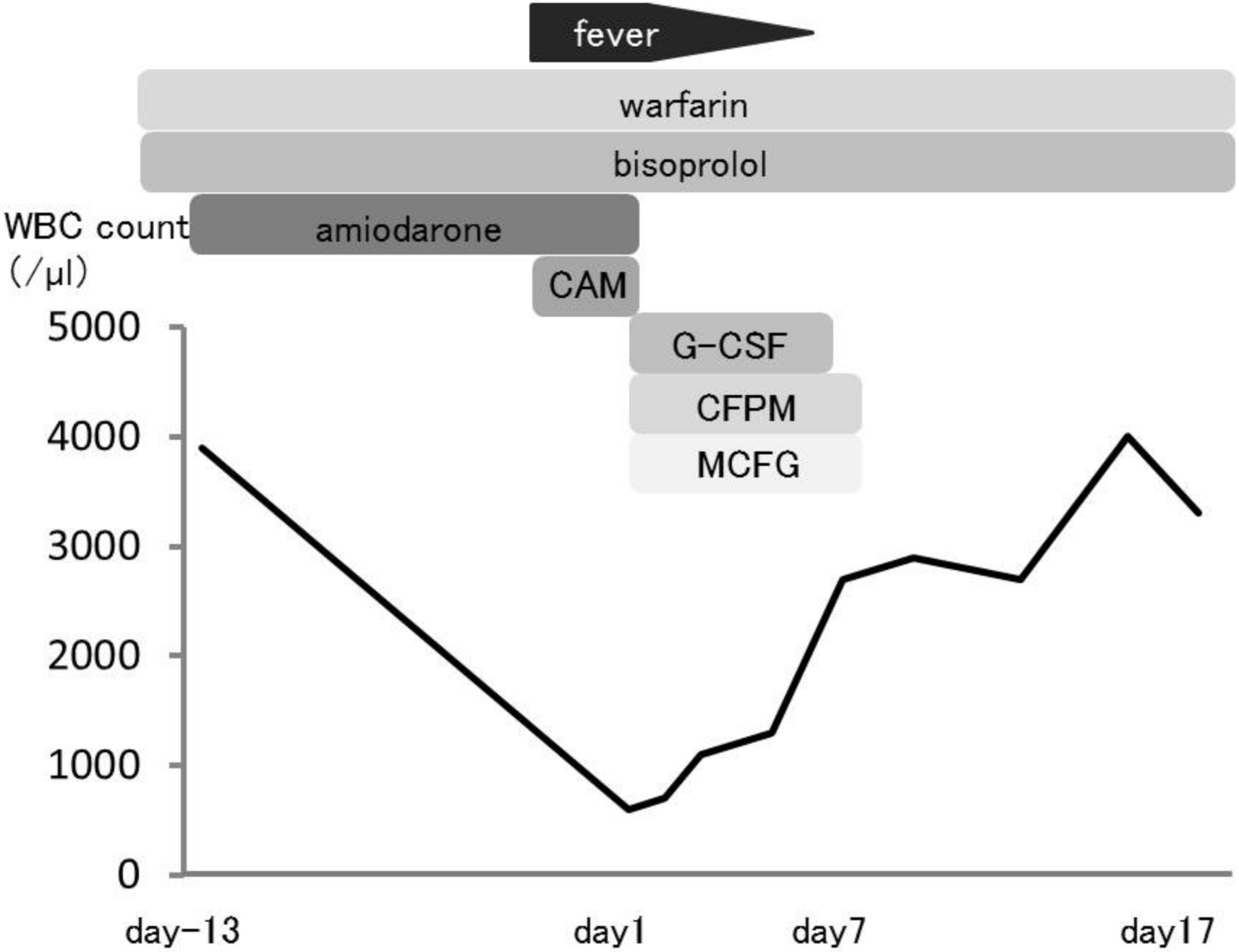
fever
warfarin
bisoprolol
amiodarone
CAM
G-CSF
CFPM
MCFG
WBC count
(/μl)
5000
4000
3000
2000
1000
0
day-13
day1
day7
day17