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Hypereosinophilic syndrome presenting as eosinophilic gastroenteritis exacerbated by clopidogrel bisulphate

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Running head: Hypereosinophilic syndrome presenting as eosinophilic gastroenteritis

Abstract

Clopidogrel is a widely prescribed prodrug with antithrombotic activity that functions by irreversibly inhibiting the P2Y12 receptors on platelets; nevertheless, drug-induced eosinophilia from this drug is rarely reported. An 81-year-old man was diagnosed with cerebral infarction 2 months earlier and was admitted to our hospital with rash, fever, wheezing, and stomach discomfort after being initiated with clopidogrel treatment. Based on his medical history, chest CT, and gastroscopy, we diagnosed him with clopidogrel-induced hypereosinophilic syndrome. After discontinuation of clopidogrel, the eosinophilia and symptoms improved. In cases of drug-induced eosinophilia, it is important to obtain a detailed medical history.

Keywords: eosinophilic gastroenteritis, eosinophilic pneumonitis, computed tomography, hypereosinophilic syndrome, gastroscopy

Introduction

Hypereosinophilic syndrome (HES) is a rare and under-reported group of diseases that are characterized by persistent eosinophilia above 1500/μL at an interval of at least 1 month apart, or pathologic confirmation of tissue hypereosinophilia and eosinophil-mediated organ damage/dysfunction [1, 2]. To make this diagnosis, causes of organ damage and secondary causes of hypereosinophilia must be ruled out [1]. HES is a group of disorders marked by the sustained overproduction of eosinophils, in which eosinophilic infiltration and mediator release cause damage to multiple organs. HES is further subclassified into primary, secondary, or idiopathic, according to the pathogenic mechanisms resulting in eosinophil expansion. Despite intensive etiological workup, the underlying causes of HES cases often remain unknown; such cases are referred to as an idiopathic HES. Thus, diagnosing the cause of HES is extremely difficult. Eosinophilic gastrointestinal disorders, including eosinophilic esophagitis, eosinophilic gastroenteritis, and eosinophilic colitis, are a group of inflammatory conditions characterized by eosinophilic infiltration of the bowel wall [3] and can occur as an isolated disorder associated with HES or as part of a multisystem HES. Herein we report a rare case of HES presenting as eosinophilic gastroenteritis exacerbated by clopidogrel bisulphate.

Case report

An 81-year-old man with high fever, wheezing, eruption, and stomach discomfort was referred to our hospital for further examination and treatment. Two months earlier, he suddenly developed gait disturbance, was diagnosed with cerebral infarction,

and was admitted to another hospital. Treatment with clopidogrel bisulphate 75 mg/day was initiated for cerebral infarction, and his symptoms gradually improved. However, eruptions appeared one month prior, and high fever, wheezing, and stomach discomfort appeared three weeks prior. At the same time, a marked increase in eosinophil count was observed. Laboratory examination at transfer revealed elevated levels of C-reactive protein (3.55 mg/dL, normal <0.15 mg/dL), immunoglobulin E (IgE) (4338.0 IU/mL, <232.0 IU/mL), and white blood cells (11200/μL, 3300-8600/μL; eosinophils, 5660/μL) (Table 1). Urinalysis showed no abnormalities. Stool samples tested negative for parasites. Infection testings including β-D-glucan, T-SPOT.TB assay (interferon-γ release assays for detection of Mycobacterium tuberculosis), hepatitis B surface antigen, and hepatitis C virus antibody were all negative. Computed tomography of the chest showed interstitial lesions, infiltration shadows and pleural effusion of both lungs (Figure 1). Findings of gastroscopy revealed erosion and swelling of the mucosa of the stomach and duodenum (Figure 2), and the findings of the biopsy tissue from the mucosa of the stomach and duodenum showed numerous eosinophil infiltrations in the submucosa (Figure 3). Thus, the patient was diagnosed with eosinophilic gastroenteritis as part of HES, with multiple organ involvement (lung, stomach, and duodenum). As shown in Figure 4, clopidogrel bisulphate was discontinued at the time of transfer because it was suspected to be the cause of his eosinophilia based on his clinical course. After discontinuation of clopidogrel bisulphate, the symptoms gradually improved, and the eosinophil count gradually normalized. Furthermore, since the exacerbation and remission of lung lesions occurred in parallel with increases and decreases in eosinophil counts

without treatment with antibiotics, steroids, or immunosuppressants, we considered that he may also have eosinophilic pneumonitis as part of the HES. A month later he was discharged without recurrence.

Discussion

HES is characterized by the presence of marked unexplained blood and tissue eosinophilia and is associated with a variety of clinical manifestations. Classical diagnostic criteria for HES have used three criteria: (a) blood eosinophilia >1500/μL for longer than 6 months (or death before 6 months associated with signs and symptoms of hypereosinophilic disease), (b) lack of evidence for parasitic, allergic, or other known causes of eosinophilia, and (c) presumptive signs of organ involvement, such as heart failure, gastrointestinal dysfunction, central nervous system abnormalities, fever, or weight loss [4]. However, because it is ethically questionable to allow a patient with symptomatic HES to develop irreversible damage without treatment for 6 months, the currently accepted definition of HES is [5, 6]: (a) blood eosinophilia of greater than 1500/mm^3 on at least 2 occasions or evidence of prominent tissue eosinophilia associated with symptoms and marked blood eosinophilia. (b) Exclusion of secondary causes of eosinophilia, such as parasitic or viral infections, allergic diseases, drug-induced or chemical-induced eosinophilia, hypoadrenalism, and neoplasms. There are 6 clinical variants of HES: myeloproliferative HES, lymphocytic variant HES, overlap HES, associated HES, familial HES, and idiopathic HES [7]. According to the latest criteria for HES, our case can be diagnosed as associated HES of secondary HES.

HES is truly a heterogeneous condition, and its actual incidence and prevalence are unknown. Based on a surveillance study, the highest estimated age-adjusted incidence rate was 0.18 per 100,000 person-years, with a prevalence of 6.3 per 100,000 person-years, and a predominant male affliction (risk ratio: 1.47) [8]. The clinical presentation of HES is highly variable, ranging from no symptoms to life-threatening cardiovascular or neurological complications, depending on the organ system involved. The presenting symptoms, in order of relative frequency, are as follows: dermatologic (37%), pulmonary (25%), gastrointestinal (14%), rheumatologic (7%), cardiac (5%), constitutional (5%), incidental (5%), neurologic (4%), and hematologic (3%) [9]. The prevalence of eosinophilic gastrointestinal disorders is estimated to be around 18 per 100,000 persons. The clinical features of eosinophilic gastrointestinal disorders differ based on (a) the layers of bowel involved, (b) location in the GI tract, and (c) degree of infiltration [8-10]. Mucosal type eosinophilic gastrointestinal disorders can present with dyspepsia, abdominal pain, nausea, vomiting, diarrhoea, protein-losing enteropathy, or malabsorption. Primary gastrointestinal disorders are rarely associated with gastrointestinal tissue eosinophilia with or without peripheral blood eosinophilia [6]. Furthermore, in patients with primary eosinophilic gastritis/gastroenteritis, the peripheral blood eosinophil count is not always abnormal [6].

Treatment of HES is tailored to the organ involved. Steroid therapy with prednisone is generally the first choice. Various tapering regimens have been studied, but there are no definitive methods, and repeated doses or long-term maintenance therapy may be required in recurrent cases. Therefore, in order to avoid unnecessary side effects

associated with long-term steroid therapy, it must be carefully considered whether treatment is indicated and, if possible, to avoid drug therapy by identifying and eliminating the cause, as in our case.

Clopidogrel is a widely prescribed prodrug with anti-thrombotic activity that functions through irreversible inhibition of the P2Y12 receptor on platelets. Many cases of hypersensitivity reactions have been reported in connection with P2Y12 inhibitors, including clopidogrel [11]; however, few of these cases have included eosinophilia [12]. The diagnosis of clopidogrel hypersensitivity is clinically based on the symptoms and timing of their appearance. Estimates of clopidogrel-induced hypersensitivity reactions and associated organ damage is often determined by the improvement of symptoms following drug discontinuation. Thus, clopidogrel also needs to be identified as a suspected drug. Moreover, our patient's condition rapidly improved after the discontinuation of clopidogrel.

In conclusion, HES is a rare and difficult-to-diagnose disease including various conditions to be differentiated. Since HES could potentially cause multiple organ failure, a thorough examination of the majority of organ systems should be performed. In addition, although there are still few reports of HES caused by clopidogrel, clinicians need to be aware that clopidogrel can cause HES and should be discontinued if HES occurs. Further reports are needed to determine how often eosinophilia is associated with hypercalcemia and to clarify the mechanism underlying the involvement of eosinophilia with hypercalcemia, including pathological findings.

Clopidogrel este un antitrombotic utilizat frecvent, el inhibând ireversibil receptorii P2Y12 plachetari. Eozinofilia asociată de la utilizarea clopdogrelului este rară. Un pacient de 81 de ani a fost diagnosticat cu AVC ischemic şi sub tratament cu clopidogrel cu 2 luni anterior prezentării la spital cu rash, febră, wheezing şi disconfort

abdominal. A fost pus diagnosticul de sindrom hipereozinofilic. După oprirea tratamentului cu clopidogrel simptomele s-au îmbunătățit și eozinofilia a scăzut. Așadar, este necesar să obținem un istoric medical detaliat.

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Figure legends

Figure 1. Findings of computed tomography of the chest

(A, B) Computed tomography of the chest showing interstitial lesions (yellow arrows), infiltration shadows (red arrows), and pleural effusion (black arrows) of both lungs.

Figure 1

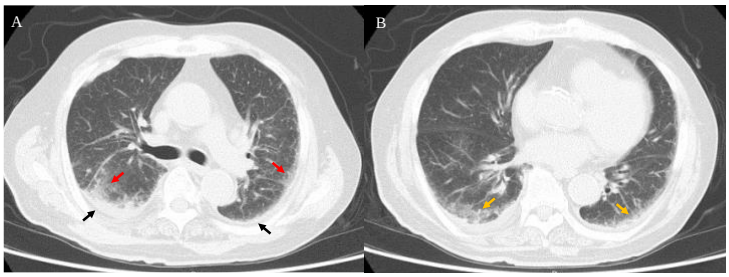

Figure 2. Macroscopic findings of the stomach and duodenum by gastroscopy

Findings of gastroscopy reveal erosion and swelling of the mucosa of the stomach and duodenum (A: gastric cardia, B: greater curvature of stomach, C: stomach pylorus, D: duodenum).

Figure 2

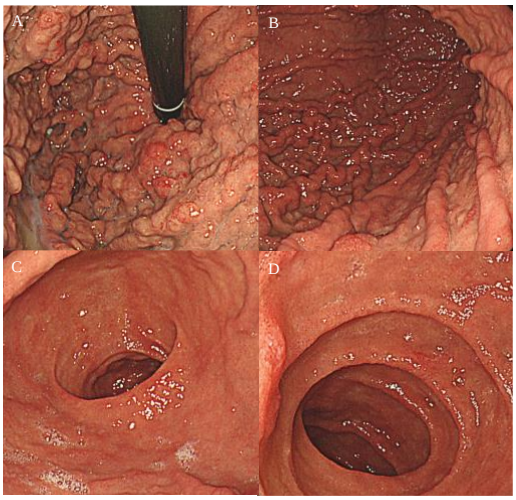

Figure 3. Histological findings of the biopsy tissue of the stomach and the duodenum

Findings of the biopsy tissue of the mucosa of the stomach and duodenum showing numerous eosinophil infiltrations (yellow arrows) in the submucosa (original magnification, stomach: A 100×, B 400×, duodenum: C: 100×, D: 400×).

Figure 3

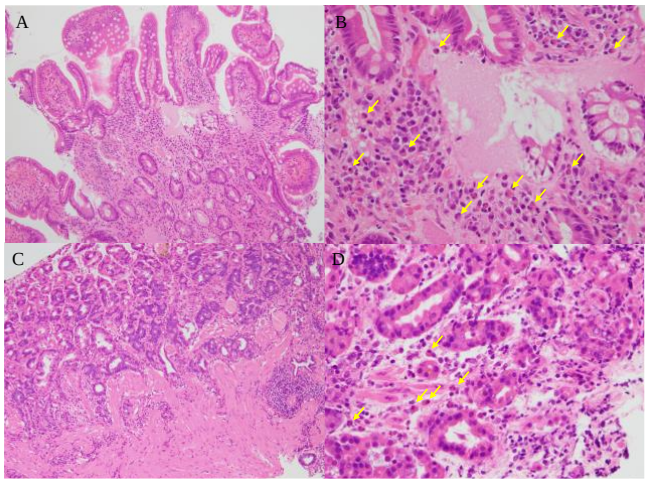

Figure 4

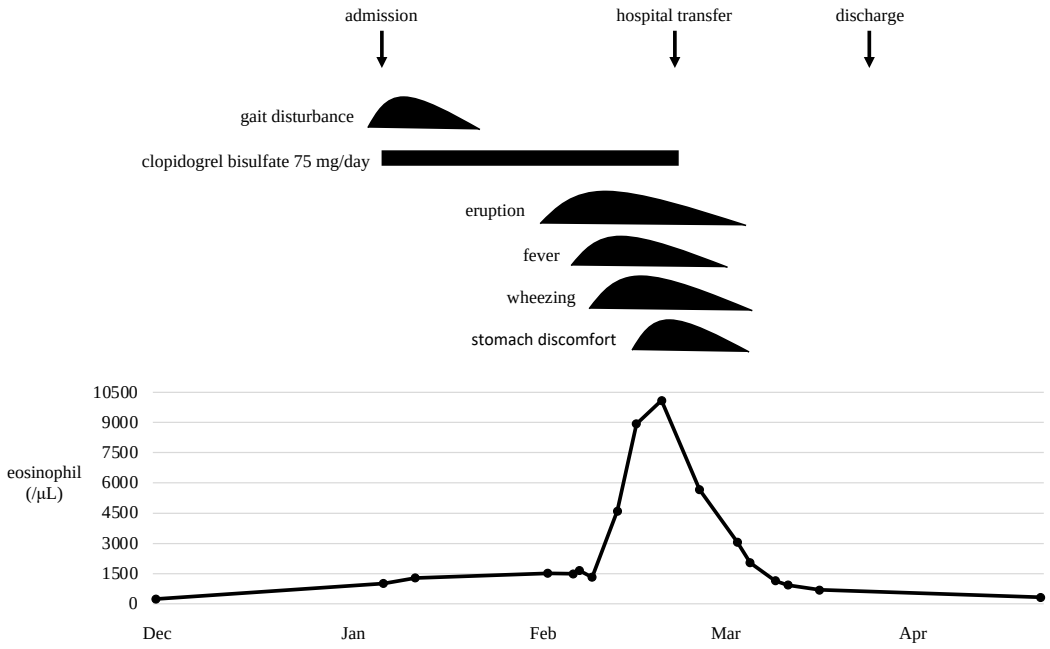

Figure 4. Clinical course of the present case.

Table 1. Laboratory findings at hospital transfer

			reference range				reference range
Alb	2.5	g/dL	4.1-5.1	WBC	11200	/μL	3300-8600
ALT	28	U/L	10-42	neut	3420	/μL	1640-5950
AST	39	U/L	13-30	lymph	1560	/μL	1120-3330
LDH	256	U/L	124-222	mono	520	/μL	180-610
Cr	0.64	mg/dL	0.65-1.07	eosino	5660	/μL	20-480
CRP	3.55	mg/dL	<0.15	baso	50	/μL	10-180
IgG	2340	mg/dL	861-1747	RBC	435	×104/μL	435-555
IgA	179	mg/dL	93-393	Hb	15.5	g/dL	13.7-16.8
IgM	98	mg/dL	33-183	Ht	39.9	%	40.7-50.1
IgE	4963	IU/mL	<232.0	Plt	49.1	×104/μL	15.8-34.8
ferritin	1061	ng/mL	39.9-465	Glu	192	mg/dL	70-140
β-D-glucan	<6.0	pg/mL	<20.0	HbA1c	6.5	%	4.9-6.0
T-SPOT	(-)			ANA	<40	×	
HBsAg	(-)			MPO-ANCA	(-)		
HCVAb	(-)			PR3-ANCA	(-)		
stool				urinalysis			
occult blood	(-)			protein	(-)		
parasites	(-)			occult blood	(-)		

Alb: albumin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, Cr: creatinine, CRP: C-reactive protein, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, IgE: immunoglobulin E, T-SPOT: T-SPOT.TB assay (interferon-γ release assays for detection of Mycobacterium tuberculosis), HBsAg: hepatitis B surface antigen, HCVAb: hepatitis C virus antibody, WBC: white blood cells count, neut: neutrophils, lymph: lymphocytes, mono: monocytes, eosino: eosinophils, baso: basophils, RBC: red blood cells count, Hb: hemoglobin, Ht: hematocrit, Plt: platelets, Glu: glucose, HbA1c: hemoglobin A1c, ANA: anti-nuclear antibody, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase-3-anti-neutrophil cytoplasmic antibody.