Synchronous malignant B-cell lymphoma and gastric tubular adenocarcinoma associated with paraneoplastic cutaneous vasculitis: hypereosinophilic syndrome with mixed cryoglobulinemia is an important sign of paraneoplastic syndrome

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Abstract

Gastric adenocarcinoma developing concomitantly with a lymphoma is rare. Furthermore, B-cell lymphoma, originating from lymph nodes, with eosinophilia is extremely rare. We report here a case with a synchronous diffuse large B-cell lymphoma (DLBCL) and an early adenocarcinoma of the stomach. In addition, this case seemed to be associated with paraneoplastic cutaneous vasculitis caused by hypereosinophilic syndrome (HES) with mixed cryoglobulinemia (MC). Many neoplastic diseases that affect internal organs display cutaneous manifestations, which may be the presenting signs and symptoms of the underlying malignancy. In particular, the association between cutaneous vasculitis and malignancy has been widely reviewed, and recently neoplasms have been suggested to produce antigens and the resultant immune complex formations, activating the serum complement, thus cause paraneoplastic vasculitis. In this case, severe eosinophilia and cryoglobulinemia with low complements were observed in a laboratory test. A biopsy specimen from a skin lesion revealed leukocytoclastic vasculitis with severe perivascular infiltration of eosinophils. The cutaneous vasuculitis was considered to be a manifestation of HES with MC, although there were no etiological factors of HES and MC. Therefore, the vasculitis seems to be a symptom of paraneoplastic syndrome in this case. Our finding suggests that the potential presence of malignancies should be kept in mind as a possible underlying disorder especially in the presence of HES with MC; this possibility is interesting also as regards at least part of the pathogenesis for paraneplastic syndrome.

Introduction

Hypereosinophilic syndrome (HES) is a clinical disorder characterized by persistent eosinophilia and systemic signs, and the cutaneous lesions are one of the common manifestations derived from HES, including vasculitis.[1] Although malignant T-cell lymphoma and other malignant tumors associated with eosinophilia have been reported sporadically,[1-3] B-cell lymphoma, originating from lymph nodes, with eosinophilia is extremely rare.[4,5] On the other hand, cryoglobulinemia is defined as the presence of circulating immunoglobulins that precipitate with cold temperature. After immunochemical typing, cryoglobulinemia is classified as type I, II, and III cryoglobulinemia. Furthermore, type II and III are defined as mixed cryoglobulinemia (MC), with a monoclonal component in type II and only polyclonal immunoglobulins in type III. Since the discovery of hepatitis-C virus (HCV) infection, it has become clear that HCV is associated with most cases of MC. In addition, MC is known to cause a systemic vasculitis and, interestingly, it has been reported that patients with non-HCV related MC vasculitis have a four-fold increased risk of developing B-cell lymphomas.[6] These data suggest the presence of MC itself is one of the risk factors for developing lymphomas. Furthermore, the association between vasculitis and malignancy has been widely reviewed, and recently neoplasms have been suggested to be a causative factor of the vasculitis.[7,8] Many reports regarding neoplastic vasculitis have been published since, thus suggesting that cutaneous vasculitis especially may appear as an initiating sign of paraneoplastic syndrome.[9-12] We report here a female patient with cutaneous vasculitis caused by HES and MC, subsequently diagnosed as synchronous diffuse large B-cell lymphoma

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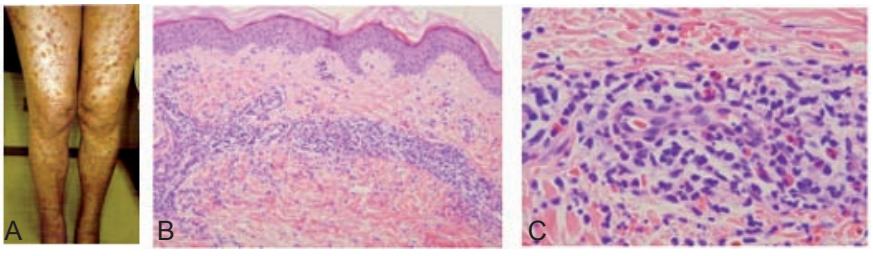

Figure 1. Skin lesions. (A) The gross appearance of purpura on the lower legs; (B, C) the histological findings of the purpura, showing massive infiltration of neutrophils and lymphocytes with deposits of fibrin on the vessel wall. Marked eosinophil and red blood cell infiltration is observed in the perivascular region. The cutaneous lesion was diagnosed as leukocytoclastic vasculitis with severe perivascular eosinophil infiltration. (Hematoxylin-eosin stain; magnification: B, 100X and C, 400X.)

(DLBCL) and early gastric cancer. Our present case is extremely rare and it suggests the requirement of surveillance of the cutaneous vasculitis for the underlying malignancies especially in the presence of HES with MC.

Case Report

A 63-year-old female visited our outpatient department because of continuous fever, purpura with pitting edema, and dysethesia in her lower legs (Figure 1A) for a month. She was admitted to our hospital for further examination. A biopsy specimen from a skin lesion revealed leukocytoclastic vasculitis with severe perivascular infiltration of eosinophils (Figure 1B). Her laboratory findings on admission are summarized in Table 1. These data revealed significant hypereosinophilia (white blood cell count [WBC], 7200 mm^3 with 52% eosinophils; normal range: 1-5%), and elevated serum levels of interleukin (IL)-4 (7.4 pg/mL; normal range: <6 pg/mL) and IL-5 (59.3 pg/mL; normal range: <10 pg/mL), which are known to be growth factors for eosinophils. Neither atypical lymphocytes nor lymphoblastic cells were recognized. The C-reactive protein (CRP) level was 0.8 mg/dL (normal range: <0.3 mg/dL), thus indicating a weak inflammatory reaction. Both titers of myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) and proteinase-3 (PR3)-ANCA were negative. The serum level of rheumatoid factor (RF) was strongly positive (751 IU/mL; normal range: <20 IU/mL) although no clinical symptoms of rheumatoid arthritis (such as tenderness or swollen joints) were observed, and antinuclear-antibody (ANA) titers and disease-specific antinuclear antibodies were negative (40X; normal range: <80X). She also demonstrated some abnormal findings such as cryoglobulinemia or decreased serum complement levels, especially the C4 component (<3 mg/dL; normal range: 13-35 mg/dL). Several days before admission, she progressively developed systemic peripheral lymphadenopathy (mediastinal, axillar, and inguinal), and her laboratory tests revealed an elevated serum level of soluble IL-2 receptor (sIL-2R). FIP1L1-PDGFRA mutation was not observed. MC is known to cause leukocytoclastic vasculitis owing to the deposition of immune complexes on the vessel wall and the activation of complements resulting in vascular damage. Therefore, we considered the cutaneous vasculitis to be a manifestation of HES with MC because of the presence of severe eosinophila and perivascular infiltration by eosinophils. Regarding the lymphadenopathy and elevated serum level of sIL-2R, we suspected the presence of malignant lymphoma or other hematological malignancies; thus, a biopsy was performed on the inguinal lymph node. The lymph node specimen showed an accumulation of CD20-positive B-cells on immunohistochemical staining (Figure 2A). Initially the patient was diagnosed with follicular lymphoma because BCL2 staining was positive (Figure 2B); however, hematoxylin and eosin (HE) staining (Figure 2C) and BCL2 staining revealed that the follicular formation was not so obvious and diffuse proliferation of the cells was recognized concomitantly. Subsequent CD10 staining was negative and genetic transformation t(14;18) was not observed (data not shown). CD10 and t(14;18) are generally highly positive in follicular lymphoma; therefore, the patient was diagnosed ultimately with DLBCL transformed from follicular B-cell lymphoma. To exclude the possibility of other types of B-cell lymphomas

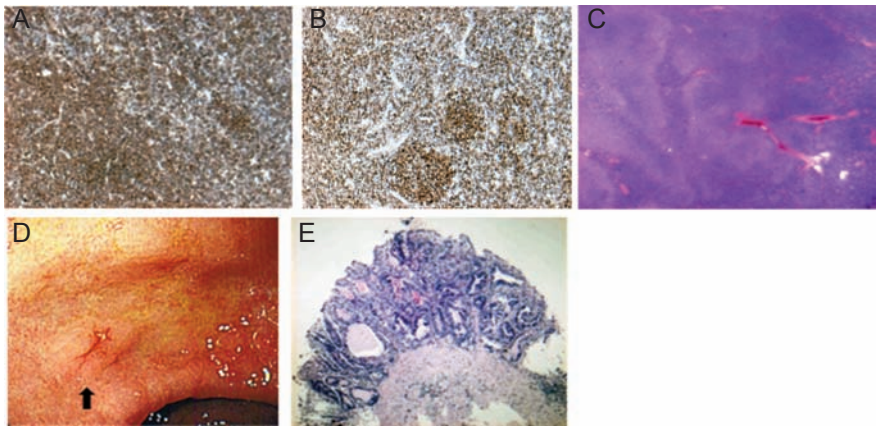

Figure 2. Biopsy specimens from lymph node (A-C) and stomach (D-E), showing anti-CD20 antibody immunohistochemical staining (A) and anti-BCL2 antibody immunohistochemical staining of the lymph node specimen (B), magnification: 40X; hematoxylin-eosin staining of the lymph node specimen (C), magnification: 12.5X; and (D) the macroscopic finding of a biopsy specimen from the gastric lesion (indicated by arrow), and (E) hematoxylin-eosin staining, magnification: 10X. The specimen from the lymph node was strongly positive for CD20 and BCL2. Hematoxylin-eosin and BCL-2 staining showed some follicular formations and diffuse proliferation of the cells concomitantly. The patient was diagnosed with DLBCL transformed from follicular B-cell lymphoma. The gastroscopy specimen revealed irregular atypical cell proliferation in the mucosa, and the patient was diagnosed with early gastric cancer (tubular adenocarcinoma).

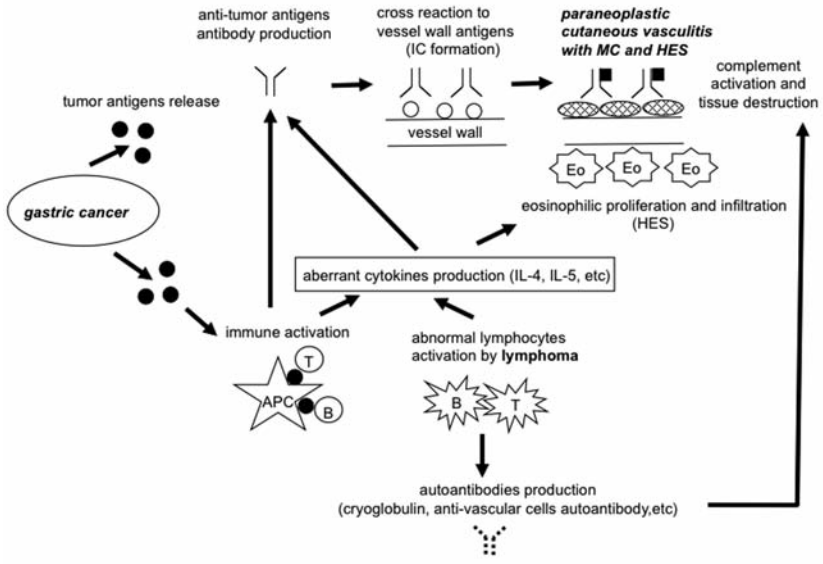

Figure 3. A schematic figure illustrating the hypothesis for paraneoplastic vasculitis with hypereosinophilic syndrome and mixed cryoglobulinemia. IC: immune complexes, APC: antigen-presenting cells, T: T-lymphocytes, B: B-lymphocytes, Eo: eosinophilia, MC: mixed cryoglobulinemia, HES: hypereosinophilic syndrome.

such as mucosa-associated lymphoid tissue (MALT) lymphoma, mantle cell lymphoma, Burkitt lymphoma, and small lymphocytic lymphoma, a gastroscopy was performed and it revealed a protruding lesion with ulceration at the lesser curvature in the corpus ventriculi (Figure 2D, left). Unexpectedly, the histological findings indicated an early stage of gastric cancer (Figure 2D, right) and the histological diagnosis was a gastric cancer, IIc, tubular adenocarcinoma (tub1), m, ly0, v0, cut margin(-), although there was no evidence of lymphoma. As a result, the patient was diagnosed with cutaneous leukocytoclastic vasculitis with synchronized occurrence consisting of DLBCL and early gastric adenocarcinoma. An endoscopic mucosal resection was performed as a treatment for her gastric cancer, and thereafter she underwent chemotherapy for the lymphoma in the hematological department of our hospital. The treatment for DLBCL was successfully accomplished using chemotherapy with a THP-COP regimen comprising cyclophosphamide, pirarubicin (tetrahydropyranyl adriamycin [THP]), vincristine, and prednisolone. The symptoms related to the cutaneous leukocytoclastic vasculitis disappeared totally.

Table 1. Laboratory findings on admission.

WBC	7900/mL	AST	15 IU/L	RF	751 IU/mL
Neutro	27.0%	ALT	6 IU/L	ANA	40X
Lympho	13.0%	ALP	362 IU/L	αDNA Ab	(-)
Mono	5.0%	LDH	271 IU/L	αRNP Ab	(-)
Eosino	52.0%	CPK	61 IU/lL	αSm Ab	(-)
AtyLy	(-)	BUN	11 mg/dL	αSS-A Ab	(-)
Blast	(-)	Crea	0.6 mg/dL	αSS-B Ab	(-)
RBC	382x10⁴/mL	UA	3.1 mg/dL	αCL,2GP1 Ab	(-)
Hb	12.4 g/dL	TP	5.9 g/dL	PR3-ANCA	(-)
Ht	35.7%	ALB	3.8 g/dL	MPO-ANCA	(-)
Plt	16.1 x	IgG	874 mg/dL	Cryogloblin	(+)
CRP	10⁴/mL	IgA	178 mg/dL	MMP-3	41.7 ng/mL
ESR	0.8 mg/dL	IgM	170 mg/dL	HCV	(-)
PT-INR	5 mm/h	IgE	43.0 mg/dL	HBV	(-)
APTT	1.18	CH50	<5 U/mL	sIL-2R	2610 U/mL
Ferritin	33.4 sec	C3	70 U/mL	IL-4	7.3 pg/mL
	191.4 ng/mL	C4	<3 U/mL	IL-5	59.3 pg/mL
Urinalysis		CEA	0.9 U/mL	ECP	2.7 μg/lL
Blood (-)		CA19-9	1.9 U/mL		
Protein (-)				*FIP1L1-*	mutation (-)
Glucose (-)				*PDGFRA*	

Discussion

It is extremely rare that HES occurs not in B-cell but in T-cell lymphomas, and that lymphoma and gastric adenocarcinoma occur simultaneously. In a MEDLINE literature search (keywords: gastric cancer, B-cell lymphoma, and vasculitis), no item was found. We believe that this is the first report of synchronous malignant B-cell lymphoma and early gastric cancer associated with paraneoplastic vasculitis caused by HES with MC. In addition, it appears clinically important for us to recognize cutaneous vasculitis as paraneoplastic syndrome. In this report, we discuss the etiology of paraneoplastic vasculitis.

The relative risk of the occurrence of solid tumors and hematological malignancies is known to be higher in autoimmune patients than in the normal population, and some autoimmune disorders can appear to be paraneoplastic syndrome before a malignant tumor is identified.[13] Several reports have indicated that vasculitis can be a paraneoplastic symptom in either hematological malignancies or solid tumors.[14-16] Vasculitis is an inflammatory condition that can affect any type of blood vessel owing to several immunologic mechanisms. The possible mechanisms of paraneoplastic vasculitis include invasion of circulating tumor cells toward the vessel wall, damage to the endothelium by cytokines released from circulating tumor cells, the cross-reaction with autoantibodies that can bind either tumor-specific antigens or endothelial antigens, and the deposition of circulating immune complexes, resulting in tissue damage because of complement-mediated cell destruction. The presence of cryoglobulin and low plasma C4 levels in our patient also indicate that circulating immune complexes may play an important role in the induction of the vasculitis. Interestingly, it has been reported that MC itself is a risk factor for lymphoma development.[16] Although MC is known to be observed frequently in patients with HCV infections, our patient did not demonstrate any antibodies or antigens for HCVs. In a case of non-HCV related MC, we should pay more attention to lymphocytic disorders or malignant tumors, which are underlying MC as reported previously.[6] Furthermore, it has been reported that hypocomplementemia is associated with lymphoma development in primary Sjogren's syndrome.[17] Our case is able to support these notions. Regarding another etiology of paraneoplastic vasculitis, tumor antigens may activate lymphocytes, thus resulting in an over-production of T-helper (TH)-2 type cytokines, such as IL-4 or IL-5, and subsequently recruiting eosinophils to the vessels; these phenomena seem to have contributed to the development of HES. In fact, higher expressions of these cytokine proteins in certain lymphoma cells have been reported.[16] HES is defined by three diagnostic criteria: eosinophils, >1.5x10⁹/L, persistent eosinophilia and/or organ damage or dysfunction, and exclusion of secondary causes of eosinophilia such as parasite infection or allergic reaction. HES is classified further as myeloproliferative HES, lymphocytic HES, familial HES, associated HES, overlap HES, and undefined HES.[18] Identification of the lymphocytic HES rests on recognition of the helper T-cell subset (especially TH2) and clonal overgrowth of specific cytokine (especially IL-5) producing cells. Although we did not confirm the T-cell clonality producing IL-5, B-cell abnormality derived from DLBCL may stimulate the T-cell clones resulting in HES.

Literature analyses indicate that characteristics of representative paraneoplastic vasculitis show cutaneous leukocytoclastic vasculitis or cryoglobulinemic vasculitis. Recently, Solans-Laque *et al*. reported that the most common vasculitis in solid tumors was leukocytoclastic vasculitis and the most common malignancies were in urinary organs, gastrointestinal tract, and lung.[19] Furthermore, they mentioned that 13 of 15 patients demonstrated concordance of disease activity and treatment response for cancer and vasculitis, apart from 46.6% cases of the vasculitis that flared up, heralding tumor recurrence or progression. They suggested that resolution of vasculitis following effective treatment of the putatively linked malignancy, and recurrence of vasculitis heralding tumor recurrence or progression, provide strong evidence for vasculitis being a true paraneoplastic syndrome, not occurring

by chance.[19] Skin purpura or papules appear to be the most common skin manifestations, while hematological malignancies such as lymphoma are the most common malignancies presenting as underlying diseases.[9-12] Our case supports these notions and reminds us that we should pay attention to the importance of performing careful examinations in order to exclude other diseases, especially malignancies that may exist as underlying causes of HES and MC, with skin involvement as an important sign of paraneoplastic syndrome.

Finally, our hypothesis regarding the pathogenesis of the paraneoplastic vasculitis in the present case is shown in Figure 3. We think two possible mechanisms for the paraneoplastic vasculitis derived from gastric cancer and lymphoma are considerable. In gastric carcinoma, tumor antigens of gastric cancer may be released into the extracellular region and recognized by the immune system as autoantigens in a particular individual, resulting in an immune activation against the tumor antigens. Once the immune system is activated, anti-tumor-antigen antibodies are produced; furthermore, aberrant cytokine production may be induced. The antibodies possibly react with vessel wall antigens by cross-reaction, resulting in the formation of immune complexes on the vessel wall. Then, complement is recruited to the immune complexes and activated, ultimately resulting in the vasculitis. The aberrant cytokine production, such as IL-4 and IL-5, can promote eosinophilic proliferation and activation resulting in HES. The eosinophilic infiltration in the perivascular region may exacerbate the symptoms of the vasulitis further. In lymphomas, the B-cell lymphomas may induce abnormal activation of the lymphocytes resulting in autoantibody production, such as cryoglobulin or anti-vascular cells autoantibody. The aberrant activation of the lymphocytes also may induce excessive IL-4 and IL-5 production. The autoantibodies may interact with the vessel wall resulting in the vasculitis as described previously. In the present case, the latter appeared to be the main factor of the vasculitis rather than the former, because the gastric cancer is at the early stage, and it is difficult to think that small early gastric cancers cause the paraneoplastic phenomenon.

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