

[CASE REPORT]

Paraneoplastic IgA Vasculitis in an Adult with Lung Adenocarcinoma

Shuji Ota¹, Terunobu Haruyama¹, Masashi Ishihara¹, Maika Natsume¹, Yoko Fukasawa¹,
Takahiko Sakamoto¹, Shigeru Tanzawa¹, Ryo Usui¹, Takeshi Honda¹, Yasuko Ichikawa¹,
Kiyotaka Watanabe¹, Yuko Sasajima² and Nobuhiko Seki¹

Abstract:

A 50-year-old man with lung adenocarcinoma (c-T1aN2M1b) experienced reddish purpura mainly on the lower legs after receiving 12 cycles of second-line chemotherapy with docetaxel. There was tumor enlargement on computed tomography performed to assess the therapeutic response, so paraneoplastic IgA vasculitis was considered. IgA vasculitis was diagnosed based on a biopsy of the skin lesion and histology of an upper gastrointestinal hemorrhagic mucosal erosion. As IgA vasculitis can lead to serious gastrointestinal or systemic complications, IgA vasculitis should be considered as a differential diagnosis for rashes in patients with malignancy.

Key words: IgA vasculitis, lung cancer, paraneoplastic vasculitis, drug eruption

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Introduction

IgA vasculitis is a form of vasculitis that affects the small blood vessels of the entire body, with manifestation of purpura on the upper and lower limbs, abdominal symptoms, arthropathy, and renal disorder. The disease typically affects children, with adult onset accounting for only 5% of all cases (1). We encountered a case of IgA vasculitis that occurred in association with tumor progression during chemotherapy for lung adenocarcinoma. IgA vasculitis as a paraneoplastic syndrome is rare. IgA vasculitis should therefore be considered in the differential diagnosis when encountering patients experiencing rash during chemotherapy.

Case Report

The patient was a 50-year-old man who had been diagnosed with stage IV primary lung adenocarcinoma (c-T1aN2M1b stage IVA; eighth edition of the tumor-node-metastasis (TNM) classification) 1 year earlier. The adeno-

carcinoma was poorly differentiated, and thyroid transcription factor (TTF)-1 was negative in immunohistochemistry. No epidermal growth factor receptor (EGFR) gene mutation or anaplastic lymphoma kinase (ALK) rearrangement was detected. First-line combination chemotherapy consisting of cisplatin and pemetrexed was performed for four cycles, with the best response assessed as 'stable disease'. Second-line chemotherapy with docetaxel was then started. While the best response was stable disease and the therapy was ongoing on an outpatient basis, on day 8 of cycle 12, the patient made an emergency visit with chief complaints of upper abdominal pain and petechiae on both lower legs (Fig. 1). This was initially considered to be drug eruption due to docetaxel, and the case was managed via outpatient observation for four days, but the petechiae worsened, and the patient was admitted for a detailed examination.

Upon admission, the patient's performance status score was 1. He was not taking any medication, and he was a never smoker. A physical examination revealed upper abdominal tenderness and palpable papular petechiae on both lower legs. Laboratory tests upon admission showed no par-

¹Division of Medical Oncology, Teikyo University School of Medicine, Japan and ²Division of Pathology, Teikyo University School of Medicine, Japan

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Correspondence to Dr. Nobuhiko Seki, nseki@med.teikyo-u.ac.jp



Figure 1. Photograph showing purpura on the lower leg at the time of admission.



Figure 2. Contrast-enhanced computed tomography of the abdomen upon admission showed wall thickening of the duodenum to the upper jejunum.

ticular abnormalities in the complete blood count, biochemistry, or coagulation parameters, and immunoglobulin quantification showed a normal IgA level of 236 mg/dL. Urinalysis showed no abnormalities, such as hematuria or proteinuria, while fecal occult blood testing was positive. Computed tomography (CT) performed upon admission revealed the primary lesion in the upper left lung lobe along with swollen mediastinal lymph nodes, showing a 30% enlargement compared with CT obtained 1 month earlier. Thus, the tumor response to docetaxel was assessed as 'progressive disease'. Duodenal and upper jejunal wall thickening was also observed (Fig. 2).

A skin biopsy of the petechial rash was performed after admission. Histology from the skin specimens showed no changes in the epidermis but did reveal perivascular infiltration of neutrophils and lymphocytes in the superficial dermis (Fig. 3A). The perivascular areas also contained fragmented nuclei, extravasation of red blood cells, and hemosiderin deposition; these findings were consistent with leukocytoclastic vasculitis (Fig. 3B). Although IgA staining using the direct fluorescent antibody technique was negative, the histological findings were compatible with IgA vasculitis. Upper gastrointestinal endoscopy revealed easily hemorrhagic mucosal erosion in the duodenum to the upper jejunum. Histology from this erosion showed perivascular infiltration of neutrophils and lymphocytes consistent with leukocytoclastic vasculitis, similar to the skin biopsy. Based on these findings, IgA vasculitis was diagnosed.

The initial treatment was watchful waiting, which led to worsening of the skin symptoms and no improvement in the abdominal symptoms. Thus, on hospital day 13, systemic corticosteroid therapy was started (20 mg oral prednisolone once daily), and the skin and abdominal symptoms promptly resolved. However, there was marked enlargement of the primary lung tumor with the onset of brain metastasis accompanied by brain edema, for which the prednisolone was subsequently continued. No relapse of IgA vasculitis occurred after the initiation of prednisolone administration.

Discussion

IgA vasculitis, formerly known as Henoch-Schönlein purpura, is an idiopathic form of vasculitis that affects the small blood vessels of the entire body and manifests with systemic symptoms mainly involving the skin, gastrointestinal tract, kidneys, and joints (1). According to the American College of Rheumatology diagnostic criteria for Henoch-Schönlein purpura, 1) clinically palpable purpura is a characteristic finding, and other criteria include 2) age ≤ 20 years at the disease onset, 3) the presence of gastrointestinal symptoms resulting from vasculitis, and 4) histopathological evidence of inflammation, mainly of small blood vessels in the affected areas of the skin, kidney, gastrointestinal tract, or other organs, along with histopathological findings of leukocytoclastic vasculitis on Hematoxylin and Eosin staining and deposits of IgA immune complexes on immunohistochemical staining. IgA vasculitis is diagnosed when at least two of these four criteria are met (2). Our patient met three of these criteria, although he was older than 20 years of age. Immunostaining of skin biopsy specimens from our patient showed no IgA deposits in the walls of the blood vessels. However, cutaneous IgA deposition is reportedly detected only in approximately 70% of all cases, as opposed to renal IgA deposition, which is detected in nearly 100% of all cases; hence. Therefore, the absence of cutaneous IgA deposits does not necessarily rule out a diagnosis of IgA vasculitis (3).

Paraneoplastic vasculitis is rare and accounts for approximately 2.5-5% of all cases of adult vasculitis (4), of which IgA vasculitis accounts for approximately 5% (5). However, the prevalence of malignancy among patients with adult-onset IgA vasculitis is as high as 29-43% (4). Malignancy in patients with IgA vasculitis is typically in the form of solid tumors, such as lung cancer (6, 7). There have been several reports of IgA vasculitis associated with pulmonary adenocarcinoma (8-10). However, this case is the first report of IgA vasculitis occurring during chemotherapy.

One suggested etiology of IgA vasculitis as a paraneo-

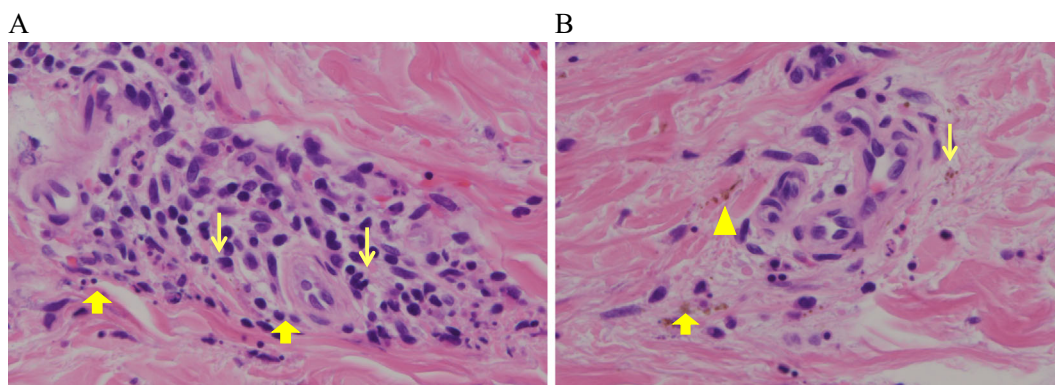


Figure 3. A histopathological examination of skin biopsy specimens from the lower leg. **A:** The superficial dermis had perivascular infiltration of neutrophils (thin arrows) and lymphocytes (thick arrows). Original magnification $\times 100$. **B:** The superficial dermis contained perivascular fragmented nuclei (thin arrow), extravasation of red blood cells (arrowhead), and hemosiderin deposition (thick arrow). Original magnification $\times 150$.

plastic syndrome is decreased clearance and overproduction of immune complexes (including IgA antibodies and tumor antigens) due to the presence of malignancy, leading to the deposition of the immune complexes in the vascular walls and mesangial areas, thereby causing inflammation (11). Another theory is that tumor cells react with antigens on the vascular endothelial cells and induce damage to the vascular walls (11). It has also been suggested that increased blood viscosity due to malignancy may play a role in the onset of the disease by promoting the deposition of immune complexes in the vascular walls (12).

Regarding the cause of IgA vasculitis in the present case, the patient had had no preceding common cold symptoms or signs of infection. Other vasculitis markers showed negative results for streptolysin O, rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibody, cryoglobulin, and rapid plasma reagin. There had been no initiation of any new medications. Thus, the onset of IgA vasculitis due to cancer progression was considered likely. IgA vasculitis did not recur in the present case despite further subsequent cancer progression, presumably due to the continued corticosteroid administration for the brain edema. IgA vasculitis reportedly responds well to corticosteroid therapy (8).

In patients with rash occurring during or after medication administration, drug eruption is considered the most likely differential diagnosis. For this reason, drug eruption due to docetaxel was initially considered in the present case. IgA vasculitis generally has a good prognosis. However, the appropriate diagnosis is necessary, as approximately 30% of patients with adult-onset IgA vasculitis have gastrointestinal symptoms and are at risk for major complications, such as intestinal perforation, necrotizing enterocolitis, and gastrointestinal hemorrhaging, which can lead to a serious outcome (13, 14). For this reason, when patients with malignancy present with a rash, clinicians should consider IgA vasculitis as a differential diagnosis and perform detailed assessments, rather than simply making a diagnosis of drug eruption based merely on the history.

The authors state that they have no Conflict of Interest (COI).

References

- Jennette JC, Falk RJ. The pathology of vasculitis involving the kidney. *Am J Kidney Dis* **24**: 130-141, 1994.
- Mills JA, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura. *Arthritis Rheum* **33**: 1114-1121, 1990.
- Pertuiset E, Lioté F, Launay-Russ E, Kemiche F, Cerf-Payrastra I, Chesneau AM. Adult Henoch-Schönlein purpura associated with malignancy. *Semin Arthritis Rheum* **29**: 360-367, 2000.
- Mitsui H, Shibagaki N, Kawamura T, Matsue H, Shimada S. A clinical study of Henoch-Schönlein purpura associated with malignancy. *J Eur Acad Dermatol Venereol* **23**: 394-401, 2009.
- Fain O, Hamidou M, Cacoub P, et al. Vasculitides associated with malignancies: analysis of sixty patients. *Arthritis Rheum* **57**: 1473-1480, 2007.
- Cairns SA, Mallick NP, Lawler W, et al. Squamous cell carcinoma of bronchus presenting with Henoch-Schönlein purpura. *Br Med J* **2**: 474, 1978.
- Maurice TR. Carcinoma of bronchus presenting with Henoch-Schönlein purpura. *Br Med J* **2**: 831, 1978.
- Mifune D, Watanabe S, Kondo R, et al. Henoch Schönlein purpura associated with pulmonary adenocarcinoma. *J Med Case Rep* **5**: 226, 2011.
- Weiler-Bisig D, Ettlin G, Brink T, et al. Henoch Schönlein purpura associated with esophagus carcinoma and adenocarcinoma of the lung. *Clin Nephrol* **63**: 302, 2005.
- Solans-Laqué R, Bosch-Gil JA, Pérez-Bocanegra C, et al. Paraneoplastic vasculitis in patients with solid tumors: report of 15 cases. *J Rheumatol* **35**: 294, 2008.
- Fortin PR. Vasculitides associated with malignancy. *Curr Opin Rheumatol* **8**: 30-33, 1996.
- Magro CM, Crowson AN. A clinical and histologic study of 37 cases of immunoglobulin A-associated vasculitis. *Am J Dermatopathol* **21**: 234-240, 1999.
- Chan JC, Li PK, Lai FM, Lai KN. Fatal adult Henoch-Schönlein purpura due to small intestinal infarction. *J Intern Med* **232**: 181-184, 1992.
- Bissonnette R, Dansereau A, D'Amico P, Pateneau J, Paradis J. Perforation of large and small bowel in Henoch-Schönlein purpura. *Int J Dermatol* **36**: 361-363, 1997.

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