Granulocyte-colony stimulating factor– and interleukin-1 β –positive cardiac myxoma accompanying neutrophilic dermatosis

Yoichi Ajiro, MD, PhD, FAPSC,^a Hitoshi Nino, MD, PhD,^b Takashi Ueda, MD,^c and Yukihiro Bonkohara, MD, PhD,^d Kanagawa, Japan

From the ^aDivision of Clinical Research, Departments of ^bClinical Laboratory and ^cDermatology, and ^dCardio-vascular Surgery, National Hospital Organization Yokohama Medical Center, Kanagawa, Japan.

Source of funding: Division of Clinical Research, National Hospital Organization Yokohama Medical Center.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Nov 18, 2019; revisions received Nov 18, 2019; accepted for publication Jan 3, 2020; available ahead of print Feb 19, 2020.

Address for reprints: Yoichi Ajiro, MD, PhD, FAPSC, Division of Clinical Research, National Hospital Organization Yokohama Medical Center, 3-60-2 Harajuku, Totsuka-ku, Yokohama-shi, Kanagawa, 245-8575, Japan (E-mail: you617bacchus@gmail.com).

JTCVS Techniques 2020;1:69-71

2666-2507

Copyright © 2020 The Author(s). Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jtc.2020.01.010>

Immunostaining of the cardiac myxoma for G-CSF (left) and IL-1 β (right).

CENTRAL MESSAGE

A cardiac myxoma may have G-CSF–, IL-1 β –, and IL-6–positive myxoma cells and could accompany afebrile neutrophilic dermatosis.

See Commentaries on pages 72 and 73.

▶ Video clip is available online.

Cardiac myxoma is the most common primary cardiac tumor.¹ Neutrophilic dermatoses are a heterogeneous group of cutaneous inflammatory conditions characterized by neutrophil accumulation in the skin. Clinically, they present with polymorphic cutaneous lesions, including pustules, bullae abscesses, papules, nodules, plaques, and ulcers.² Various cytokines and growth factors have been associated with both entities.¹⁻³

CLINICAL SUMMARY

This study was conducted with the patient's written informed consent and our institutional review board approval. A 68-year-old woman was referred to our hospital for lower-limb erythema with fever (Figure 1, A). We noted multiple, walnut-sized erythemas with induration and purpura, partially accompanied by thumb-sized bullae. The erythemas were resistant to epinastine, suplastat, and dexamethasone. The patient's fever was resistant to empiric antibiotics, and no pathogenic bacteria were detected through cultivation tests. Blood examination revealed neutrophil-dominant leukocytosis and elevated interleukin (IL)-6. A skin biopsy showed inflammatory cell infiltration, mainly composed of neutrophils, from the epidermis to the pannicle and subepidermal blister, without any evidence of necrotizing angitis (Figure 1, B-D). The systemic

examination, including transthoracic and transesophageal echocardiography, revealed a mobile caulescent cardiac tumor in the left atrium (Video 1). Cardiac tumor resection was undertaken. The tumor was 3.5 × 2.3 × 2.2 cm (Figure 2, A) in size. Pathologic examination confirmed the diagnosis of left atrial myxoma (Figure 2, A and B). Immunostaining of the myxoma specimen was positive for granulocyte colony-stimulating factor (G-CSF), IL-6, and IL-1 β (Figure 2, C-E). Following the operation, the patient was free from fever of unknown origin and neutrophilic dermatosis, and she did not develop any autoimmune diseases or malignancies for 65 months after the tumor resection.

DISCUSSION

The present case is the first reported example of a cardiac myxoma with G-CSF–, IL-1 β –, and IL-6–positive myxoma cells and accompanying neutrophilic dermatoses. Various cytokines and growth factors, such as vascular endothelial growth factor, basic fibroblast growth factor, monocyte chemotactic protein-1, and IL-6, are thought to be involved in the growth and angiogenesis of cardiac myxomas.¹ In addition, elevated plasma granulocyte-macrophage colony stimulating factor, IL-1 β , and IL-6 levels have been reported in large cardiac myxomas.³ Similarly, G-CSF,

FIGURE 1. Erythema on the lower limbs (A), and histologic examination of a skin lesion with erythema (B, ×100; C, ×400; D, ×400) showing neutrophil infiltration from epidermis to the panniculus.

FIGURE 2. Histologic examinations of the cardiac myxoma. The resected cardiac myxoma (A). Hematoxylin staining shows myxoma cells and myxoid stroma (B, ×400). Immunostaining for interleukin-6 (C, ×400), granulocyte colony-stimulating factor (D, ×400), and interleukin-1 β (E, ×400) shows brown each cytokine-positive myxoma cells.

VIDEO 1. A transesophageal echocardiogram revealed cardiac myxoma during the systemic inspection of afebrile neutrophilic dermatosis. Video available at: [https://www.jtcvs.org/article/S2666-2507\(20\)30027-4/fulltext](https://www.jtcvs.org/article/S2666-2507(20)30027-4/fulltext).

granulocyte-macrophage colony-stimulating factor, interferon-gamma, IL-1, IL-3, IL-6, and IL-8 are cytokines and growth factors potentially involved in the pathogenesis of neutrophilic dermatoses.² Among these, G-CSF is thought to play an important role in the development of neutrophilic dermatosis because neutrophilic dermatosis can accompany a G-CSF-producing tumor or recombinant G-CSF therapy.² Many types of malignancies from various organs can have G-CSF-producing properties. However, to the best of our knowledge, no G-CSF-producing cardiac myxoma has been previously reported. The present case displayed transient neutrophil-dominant leukocytosis without infection and with neutrophilic dermatosis, G-CSF- and IL-1 β -positive myxoma cells, and no neutrophil-dominant leukocytosis or neutrophilic dermatosis after tumor resection; thus, the cardiac myxoma in the present case could have been producing G-CSF and/or IL-1 β .

G-CSF is produced mainly by monocytes, macrophages, fibroblasts, and vascular endothelial cells in humans. It acts as a signal that stimulates hematopoietic precursor cells, introduces the production of granulocytes, and mobilizes peripheral blood progenitor cells for harvesting. G-CSF has also been found to play a role in tumor growth and angiogenesis in G-CSF-producing tumors. Because IL-1 and IL-6 are also involved in tumor growth via inflammation,⁴ our observation suggests possible involvement of G-CSF and IL-1 β in myxoma growth in the present case, in addition to IL-6. Interestingly, many reports have demonstrated the connections among G-CSF, IL-1, and IL-6, supporting our observation: G-CSF promotes IL-6 production and causes fever in patients with G-CSF-producing tumors; IL-1 and IL-6 production was reported in nude mice with transplanted CSF-producing tumor cell lines⁵; IL-6 promotes G-CSF production; the nuclear factors for the IL-6 gene function as promoters of G-CSF for IL-1 β response; and IL-1 β promotes IL-6 production and neutrophil activation via macrophage stimulation.⁵

In conclusion, the present case demonstrates: (1) the potential involvement of G-CSF and IL-1 β in cardiac myxomas; and (2) that neutrophilic dermatosis could be a manifestation of cardiac myxoma. Further research should explore the implications of growth factor and cytokine-producing cardiac myxomas.

References

1. Amano J, Kono T, Wada Y, Zhang T, Koide N, Fujimori M, et al. Cardiac myxoma: its origin and tumor characteristics. *Ann Thorac Cardiovasc Surg.* 2003;9:215-21.
2. Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis.* 2007;2:34.
3. Soeparwata R, Poeml P, Schmid C, Neuhof H, Scheld HH. Interleukin-6 plasma levels and tumor size in cardiac myxoma. *J Thorac Cardiovasc Surg.* 1996;112:1675-7.
4. Garlanda C, Dinarello CA, Mantovani A. The interleukin-1 family: back to the future. *Immunity.* 2013;39:1003-18.
5. Demetri GD, Zenzie BW, Rheinwald JG, Griffin JD. Expression of colony-stimulating factor genes by normal human mesothelial cells and human malignant mesothelioma cells lines in vitro. *Blood.* 1989;74:940-6.