Necrotizing fasciitis caused by *Haemophilus influenzae* type b in a patient with rectal cancer treated with bevacizumab: a case report

Tomotaka Ugai¹², Masataro Norizuki¹³, Takahiro Mikawa¹, Goh Ohji⁴, Makito Yaegashi¹

1) Division of General Internal Medicine and Infectious Disease, Department of Medicine, Kameda Medical Center, Kamogawa-shi Chiba 296-8601, Japan

2) Current address; Division of Hematology, Department of Medicine, Saitama Medical Center, Jichi Medical University, Amanuma-cho, Omiya, Saitama-shi, Saitama 330-8503, Japan

3) Current address; Department of Infectious Disease, Jichi Medical University, Shimotsuke, Tochigi 329-0498, Japan

4) Division of Infectious Disease, Department of Microbiology and Infectious Diseases, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan

**Key words:** necrotizing fasciitis; *Haemophilus influenzae* type b; bevacizumab

**Running title:** *Haemophilus influenzae* type b necrotizing fasciitis

Correspondence should be addressed to:

Tomotaka Ugai, MD

Division of Hematology, Department of Medicine, Saitama Medical Center, Jichi Medical University

1-847 Amanuma-cho, Omiya, Saitama-shi, Saitama 330-8503, Japan

Phone: +81-48-647-2111, Fax: +81-48-648-5188

E-mail address: harukakanata58@yahoo.co.jp

Alternate corresponding author: Makito Yaegashi, myaegashi@hotmail.com
Abstract:

Background:

Recently, necrotizing fasciitis has been reported in patients treated with bevacizumab, usually secondary to wound healing complications, gastrointestinal perforations, or fistula formation. The risk of invasive *Haemophilus influenzae* type b infection is significantly increased by immunocompromised hosts. However, necrotizing fasciitis due to *Haemophilus influenzae* type b with a patient treated with bevacizumab has not been previously reported.

Case presentation:

A 59-year-old woman was admitted to the intensive care unit after sudden onset of fever, chills, and right thigh pain. She received chemotherapy with fluorouracil, irinotecan, and bevacizumab for colon cancer 10 days prior to admission. The advancing erythematous margin and her worsening clinical condition necessitated an orthopedic consultation for the biopsy of the fascia. The biopsy of the frozen section showed acute necrotizing suppurative inflammation, and Gram staining of the exudates from the infected site showed the presence of gram-negative rods. After 2 days, the final results of the blood and exudate cultures confirmed the presence of *Haemophilus influenzae* type b. A diagnosis of necrotizing fasciitis was made. The patient required recurrent surgical debridement and drainage, but she recovered from the septic shock.

Conclusions

We report a case of necrotizing fasciitis due to *Haemophilus influenzae* type b in a patient without injury and with rectal cancer treated with bevacizumab. Physicians should consider invasive *Haemophilus influenzae* type b disease in the presence of necrotizing fasciitis in patients treated with bevacizumab.
Background:

Bevacizumab is an antibody designed to inhibit vascular endothelial growth factor, which is involved in blood vessel formation. Bevacizumab is quite a unique drug that is used primarily in the cancer field for the treatment of colorectal cancer and works by preventing the formation of blood vessels that feed tumors. Recently, necrotizing fasciitis has been reported in patients treated with bevacizumab, including some fatal cases[1]. However, necrotizing fasciitis usually develops secondary to wound healing complications, gastrointestinal perforations, or fistula formation. Here, we report a case of necrotizing fasciitis due to *Haemophilus influenzae* type b (Hib) in a patient without injury and with rectal cancer treated with bevacizumab.

Case presentation:

A 59-year-old woman was admitted to the intensive care unit after sudden onset of fever, chills, and right thigh pain. She had undergone low anterior resection for colon cancer 2 years earlier. After local recurrence, she underwent radiation therapy (30 Gy) for spinal metastasis followed by chemotherapy, which commenced 6 months prior to admission to the intensive care unit. She received chemotherapy with fluorouracil, irinotecan, and bevacizumab 10 days prior to admission. She was hypotensive, tachycardiac and tachypneic in the emergency room. The results of the physical examination were normal except for erythema in her right thigh. She had no previous injuries. Hemoglobin level was 118 g/L with a white blood cell count of $2.1 \times 10^9$ cells/liter and a platelet count of $1.3 \times 10^{11}$ cells/liter. Blood urea nitrogen was 18.9 mmol/L, creatinine was 318.2 µmol/L, and her C-reactive protein level was $3.8 \times 10^6$ µg/L. The results of other blood tests and urinalysis were normal. Computed tomography of the chest, abdomen, and pelvis showed normal results. Septic shock was suspected and managed accordingly with supportive measures, such as the use of a vasopressor and supplemental oxygen. Blood cultures were collected, and empirical treatment with meropenem (1 g every 12 hours) and vancomycin (1 g daily) were initiated, adjusted to renal dysfunction. The advancing erythematous margin and her worsening clinical condition necessitated an orthopedic consultation for the biopsy of the fascia. The biopsy of the frozen section showed acute necrotizing suppurative inflammation, and extensive debridement was performed. Gram staining of the exudates from the infected site showed the presence of gram-negative rods. On the following day, gram-negative rods were also isolated from the blood cultures. After 2 days, the final results of the blood and exudate cultures confirmed the presence of β-lactamase-negative Hib that was susceptible to ampicillin,
Necrotizing fasciitis was confirmed histopathologically with the debrided tissue, resulting in a diagnosis of necrotizing fasciitis due to Hib. The patient required recurrent surgical debridement and drainage, but she recovered from the septic shock. The treatment was changed to ampicillin, and she received intravenous ampicillin for a total of 51 days. She recovered completely and was discharged from the hospital 65 days after admission. Necrotizing fasciitis did not recur; however, she died of metastatic colorectal cancer 6 months after discharge.

**Discussion:**

Necrotizing fasciitis is a rare but life-threatening infection of the soft tissue that is characterized by rapidly spreading necrosis of the superficial fascia and subcutaneous tissue. Immunocompromised and diabetic patients are at a higher risk of developing necrotizing fasciitis[2]. Although bevacizumab suppresses the immune system[3], chemotherapy administered concurrently with bevacizumab is more likely to be responsible for immune suppression. This combined treatment also contributes to impaired wound healing. Therefore, the combined treatment modality is likely to place patients at an increased risk of developing necrotizing fasciitis. Despite the fact that necrotizing fasciitis is a rare complication, affecting only 1 in 5000 bevacizumab users, physicians should bear in mind the risk of necrotizing fasciitis when prescribing bevacizumab.

In a comprehensive safety review conducted by the company Roche, 52 case reports of serious necrotizing fasciitis were identified that occurred between November 1997 and September 2012 in patients treated with bevacizumab for cancer. The majority of the patients described in case reports have gastrointestinal perforations, fistula formation, or wound healing complications preceding the development of necrotizing fasciitis[4]. However, in the present case, the patient had no previous injury or risk factor for necrotizing fasciitis such as a decubitus ulcer, diabetes, or liver cirrhosis; her recent chemotherapy is her primary risk for necrotizing fasciitis. These findings suggest a possible association between necrotizing fasciitis and bevacizumab in the absence of a previous injury.

It is of particular interest that Hib caused the necrotizing fasciitis in the present case. Prior to routine Hib vaccination, Hib was a well-known cause of invasive diseases, such as meningitis and pneumonia with bacteremia, in children younger than 2 years. However, the incidence of invasive *H. influenzae* disease, especially among persons aged over 65 years, and invasive nontypable *H. influenzae* disease has increased from 1996 to 2004[5]. The risk of invasive Hib infection in adults is significantly increased by multiple
myeloma and chronic renal failure[6]. We caution physicians to consider invasive *Haemophilus influenzae* type b disease in patients treated with bevacizumab.

A review of the current literature resulted in only 4 reported cases of necrotizing fasciitis caused by Hib. The first reported case occurred in a 13-month-old infant[7] while the second case occurred in an 81-year-old man with diabetes mellitus[8]. A 64-year-old woman who developed necrotizing fasciitis of her chest wall secondary to epiglottitis represented the third case[9]. In the fourth case, a 44-year-old man developed necrotizing fasciitis of the right lower extremity after intramuscular injections of paracetamol in his right buttock[10]. Including our case, all of the patients with necrotizing fasciitis due to Hib made a full recovery. Hib merits additional consideration when deciding on appropriate, empiric antimicrobial therapy as an adjunct to surgical intervention for necrotizing fasciitis, especially in immunocompromised patients treated with bevacizumab.

**Conclusions**

We report a case of necrotizing fasciitis due to Hib in a patient without injury and with rectal cancer treated with bevacizumab. Physicians should consider invasive Hib disease in the presence of necrotizing fasciitis in patients treated with bevacizumab.

**Consent**

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**List of abbreviations**

Hib : *Haemophilus influenzae* type b

**Competing interests**

All authors declare no conflict of interests.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.
Author details

1) Division of General Internal Medicine and Infectious Disease, Department of Medicine, Kameda Medical Center, Kamogawa-shi Chiba 296-8601, Japan

2) Current address; Division of Hematology, Department of Medicine, Saitama Medical Center, Jichi Medical University, Amanuma-cho, Omiya, Saitama-shi, Saitama 330-8503, Japan

3) Current address; Department of Infectious Disease, Jichi Medical University, Shimotsuke, Tochigi 329-0498, Japan

4) Division of Infectious Disease, Department of Microbiology and Infectious Diseases, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan

Authors’ contributions

All authors have been involved in patient clinical care, and in acquisition and interpretation of data. TU have been involved in drafting the manuscript. All authors read and approved the final manuscript.
References


