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Recurrent erysipelas led to diagnosis of hereditary hemorrhagic telangiectasia

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SUMMARY

Hereditary hemorrhagic telangiectasia (HHT) is a risk of infection, such as by brain abscess associated with pulmonary arteriovenous malformations. However, association between HHT and recurrent erysipelas is not well described. HHT can cause vessel malformations in organs, leading to various serious outcomes. Prophylactic treatment is effective, but many people with HHT are undiagnosed. HHT is not described as a risk factor for soft tissue infection, but may increase the risk of serious infections requiring hospitalization.
Our 72-year-old female patient was admitted for recurrent erysipelas. Pulmonary nodules indicated pulmonary arteriovenous fistula on chest computed tomography. By recognizing this combination, although seemingly unrelated problems, we could diagnose HHT and the patient could receive adequate treatment to prevent life-threatening events.
The recurrent erysipelas was likely associated with HHT. Recurrent erysipelas is an important presentation which may facilitate early diagnosis of HHT.

Keywords: pulmonary arteriovenous malformations, epistaxis, Osler-Weber-Rendu disease

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant disorder characterized by vessel malformations (VM). If untreated, it could lead to life-threatening events including brain abscess, stroke, and pulmonary hemorrhage. Many cases of HHT are undiagnosed and some reports suggest that over 90% of people with HHT in the United States are likely undiagnosed [1]. A long diagnostic delay of HHT was reported in a retrospective study, during which 9.4% patients had severe complications [2]. Early diagnosis and treatment of HHT can prevent serious outcomes, so it is important to find undiagnosed cases.
HHT is not generally described as a risk factor for soft tissue infection, but there are reports suggesting that it can represent a high risk factor of infection for brain abscesses, and there have been reports describing certain soft tissue infections (6.5%), including abscesses and erysipelas (9.0%) [3-6]. Full examination is important to ascertain the diagnosis and to provide the patient with appropriate information, especially as their family members may also have HHT.
Our 72-year-old female patient was admitted for recurrent erysipelas, which contributed to diagnosis of HHT after an approximately 60-year delay from the onset, and which led to her treatment and examination of her family by specialists.

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CASE REPORT

The patient presented fever and impaired consciousness. Eight months previously she had been admitted to another hospital with erysipelas on the face. On the day of current presentation, she had been in her usual state of health in the morning, but she was found sitting outside and having difficulty in standing up. At this point she had diabetes for eight years and took metformin and vildagliptin. She had never smoked, did not drink alcohol, and had no known allergies. Her father had died from a stroke at the age of 74 years. On hospital evaluation, she could not focus her attention and gave only short responses. Glasgow Coma Scale was E3V4M6. Body temperature was 38.1°C, blood pressure 122/78 mmHg, pulse rate 88 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation was 96% on breathing ambient air. The body-mass index was 24.5. Physical examination showed a rash with clear border on the entire face with left superiority, involving the ear (Milian's ear sign), some blisters on the left of the face (Figure 1), and petechiae on the right eyelid. There was mottling on both lower legs and scratches on the knees. There was no Osler node, Janeway lesion, or telangiectasia on the skin, lips, or oral mucosa and no neck stiffness. Oral hygiene was good and there were no dental cavities. The remainder of physical examination (including the central nervous system) was normal.

Blood tests revealed leukocytosis and neutrophilia with leukocyte count of 10,610/μL and neutrophils accounting for 91.4%. The patient had C-reactive protein of 2.4 mg/dL and serum lactate level of 2.4 mmol/L. Urinary test and cerebrospinal fluid (CSF) test revealed no abnormalities. Cultures of blood, urine and CSF showed no growth. Whole-body plane computed tomography (CT) was performed to screen for trauma and source of infection because detailed history could not be obtained because of her altered mental status and lack of witnesses. CT showed no fractures or hemorrhage, but head CT showed old cerebral infarction in the right frontal lobe and right cerebellum without subcutaneous vasodilation. Chest CT revealed clear-bordered nodules with feeding and draining vessels in both the right S3 (13x11x8 mm) and left S8 (21x9x9 mm), suggesting pulmonary arteriovenous malformations (PAVM) (Figure 2).

Based on the skin findings and impaired consciousness, diagnosis was erysipelas on the face with sepsis. On the first hospital day, cefazolin

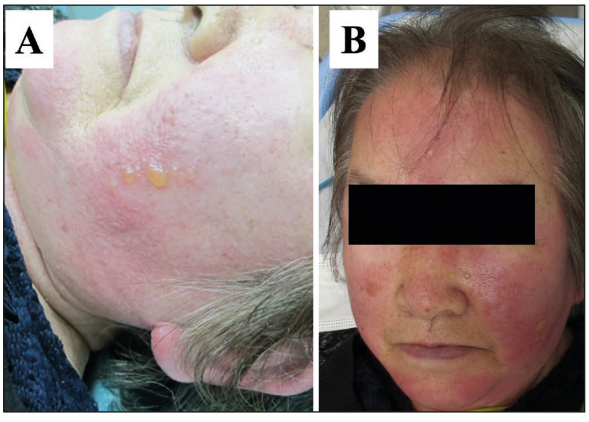

Figure 1 - Physical examination showed rash with clear border on the entire face with left superiority, involving the ear (Milian's ear sign) and some blisters on the left face.

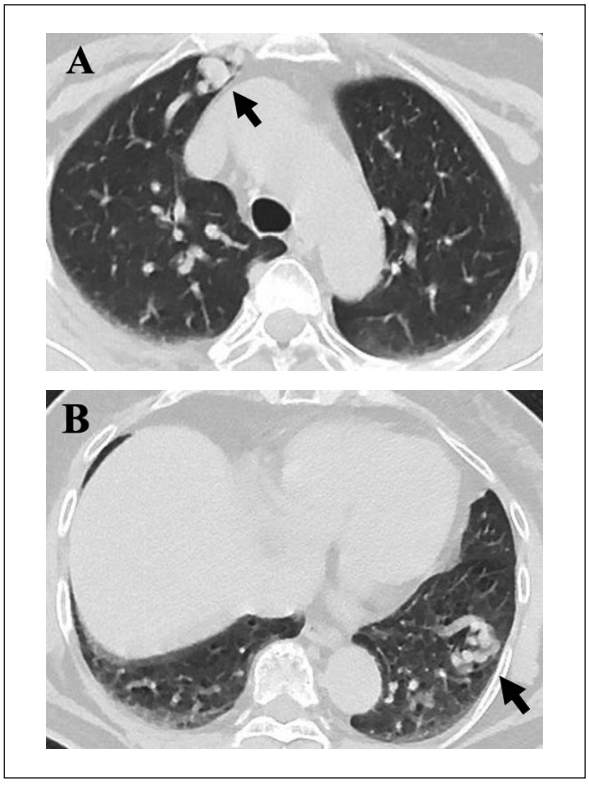

Figure 2 - Chest CT reveals clear-bordered nodules with feeding and draining vessels in both the right S3 (A) and left S8 (B), suggesting pulmonary arteriovenous malformations (arrows).

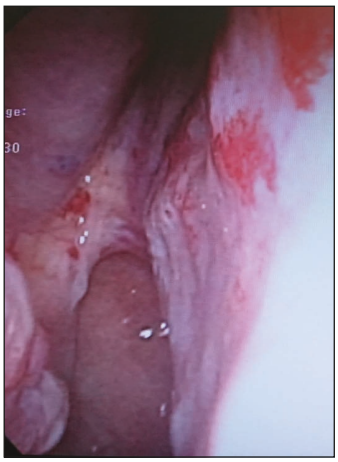

Figure 3
Nasopharyngoscopy reveals telangiectasia on the nasal mucosa.

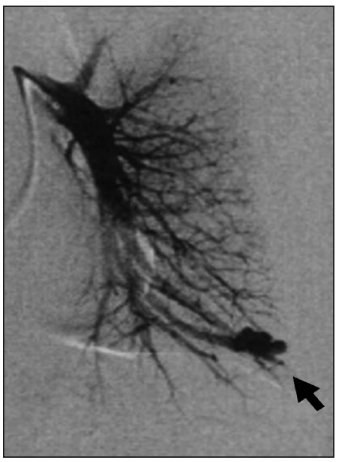

Figure 4
Pulmonary angiogram fluoroscopic image shows left S8 pulmonary arteriovenous malformations (arrow).

2 g every eight hours was administered i.v and consciousness improved within a few hours. On the third hospital day, the antimicrobial agent was switched to oral cephalexin 500 mg three times a day with improvement of skin lesions, and treatment was completed after 6 days of administration.

Nodules suggesting PAVMs had been also detected on chest CT 14 years prior to this admission, but no further examination was performed at the time. The patient did not remember the purpose for the CT and medical records were unavailable. Considering the possibility of HHT, additional medical history was taken. The patient had recurrent epistaxis since childhood. Her daughter and son also had recurrent epistaxis. Nasopharyngoscopy performed on the fifth hospital day revealed telangiectasia on the nasal mucosa (Figure 3). Nasal telangiectasia and PAVMs, HHT was thus diagnosed according to Curaçau's criteria [7]. The patient was referred to a special center for HHT and underwent catheter embolization for PAVMs (Figure 4). No other VMs were found by organ screening. Her family members underwent nasopharyngoscopy and a daughter also had telangiectasia on the nasal mucosa, confirming she also had HHT. Genetic testing was not performed for either the patient or her family after counseling.

DISCUSSION

Admission for recurrent erysipelas contributed to diagnosis and treatment of HHT before the development of life-threatening complications. The patient's family were also screened, and a daughter was also diagnosed with HHT.

The association between HHT and infectious disease is underestimated, but the risk of serious infections requiring hospitalization is probably high in people with HHT, reported at 13.6-31.0% [5, 6]. Suggested reasons include lack of the filtering function of the pulmonary capillaries due to PAVMs, the identified HHT genes encoding proteins associated with TGF-β signaling, iron metabolism problems associated with bleeding and their management, and secondary immunodeficiency related to some of the drugs used for patients with HHT, such as bevacizumab [8-10]. In a retrospective study of 353 patients with HHT, cerebral infections were associated with the presence of PAVMs, whereas extracerebral infections were associated with a longer total bleeding time of epistaxis [6]. Nasal mucosa could therefore be an entry point for infection. Skin infections have been reported to account for 8.9-27% of serious infections [5, 6]. Our patient had recurrent epistaxis and did not have clear entry for bacteria such as skin barrier disruption, edema, or poor oral hygiene. She did not have iron-deficiency anemia or any immunosuppressives drugs for HHT. After the diagnosis of HHT, there has been no recurrence of either epistaxis or erysipelas. One possible reason for the cessation of epistaxis in the patient is that she began to wear masks as a measure against COVID-19, which created a humidified environment in the nasal mucosa [11]. There has also been no recurrence of erysipelas, so cessation of epistaxis possibly contributed it. HHT may possibly have been associated with recurrent erysipelas in this patient.

Decreased life expectancy has been shown in patients with HHT that did not undergo screening or treatment compared with people without HHT [12-14]. Endoglin mutations were significantly associated with earlier death (Hazard Ratio 1.34) [13]. Life expectancy of patients with HHT screened for HHT-related organ lesions and treated as needed was similar to that of the control group [14]. In a study of 262 pregnancies, the rates of complications were 1.0% for major PAVM bleeds, 1.2% for strokes, and 1% for maternal deaths. In women experiencing a life-threatening event, prior awareness of HHT or diagnosis of PAVMs was associated with improved survival [15]. Benefits of screening and treatment have been recognized, but up to 90% of people with HHT in the United States are undiagnosed [1]. In Japan, the number of people registered with intractable disease was 445 in 2017, which is very different from the estimated number, 15,000-25,000 [16]. Most people with HHT in Japan are therefore also likely undiagnosed. A retrospective study from Italy reported that definite diagnosis of HHT was obtained after a 25.7-year delay from the onset of manifestations, during which 9.4% of patients had severe complications and 8.5% of cases were secondary to large cerebral VMs, colonic VMs and PAVMs, which could have likely been avoided by appropriate preventive treatment [2]. A Japanese study showed that only 1.3 patients were diagnosed who had family members with confirmed HHT, the average family consisting of 5.4 members [17]. Considering autosomal dominancy, family members of patients with HHT are also likely to be undiagnosed. In this case, family members underwent screening, resulting in the daughter's diagnosis of HHT. It is important to explain the characteristics of genetic diseases not only to patients with HHT, but also to their families and to help them to understand the importance of screening in order to find undiagnosed individuals with HHT within their families.

In this case, there was an approximately 60-year delay from the onset of recurring epistaxis in childhood to the diagnosis at the age of 72. The recurrent epistaxis which indicated HHT was not sufficiently severe for the patient that she sought consultation from a physician. Secondly, the pulmonary nodules found 14 years before this presentation had been overlooked because the CT was performed for an unknown other reason.

The important factors leading to the diagnosis of HHT in this patient were the constellation of seemingly unrelated problems: recurrent erysipelas, recurrent epistaxis in the patient's family history, and incidental findings of chest CT. For infectious diseases specialists and primary care physicians who are likely to encounter erysipelas, it is important to upstream the etiology of erysipelas to diagnose rare diseases such as HHT.

In conclusion, HHT in our patient was suspected from recurrent erysipelas and PAVMs, which led to diagnosis and treatment after taking additional history and further examination. Despite the benefits of screening and prophylactic treatment shown previously, HHT still has a long diagnostic delay. It is important to upstream the etiology of erysipelas for diagnosis of rare diseases such as HHT.

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Conflict of interest

The authors have no conflict of interests to declare.

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Informed consent

Written informed consent to publication of the details of this case and the accompanying images was received from the patient.

REFERENCES

[1] Sekarski LA, Spangenberg LA. Hereditary hemorrhagic telangiectasia: children need screening too. *Pediatr Nurs*. 2011; 37 (4), 163-8.

[2] Pierucci P, Lenato GM, Suppressa P, et al. A long diagnostic delay in patients with Hereditary Haemorrhagic Telangiectasia: a questionnaire-based retrospective study. *Orphanet J Rare Dis*. 2012; 7, 33.

[3] Bystritsky R, Chambers H. Cellulitis and soft tissue infections. *Ann Intern Med*. 2018; 168 (3), ITC17-ITC32.

[4] Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis*. 2014; 59 (2), 147-59.

[5] Guilhem A, Malcus C, Clarivet B, et al. Immunological abnormalities associated with hereditary haemorrhagic telangiectasia. *J Intern Med*. 2013; 274 (4), 351-62.
[6] Dupuis-Girod S, Giraud S, Decullier E, et al. Hemorrhagic hereditary telangiectasia (Rendu-Osler disease) and infectious diseases: an underestimated association. *Clin Infect Dis*. 2007; 44 (6), 841-5.
[7] Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for Hereditary Hemorrhagic Telangiectasia (Rendu-Osler-Weber Syndrome). *Am J Med Genet*. 2000; 91, 66-7.
[8] Rodríguez-García J, Zarrabeitia-Puente R, Fernández-Santos R, García-Erce JA. Infection prevention in patients with hereditary hemorrhagic telangiectasia. *Haematologica*. 2018; 103 (10), e491-e2.
[9] Kumar V, Choudhry VP. Iron deficiency and infection. *Indian J Pediatr.* 2010; 77 (7), 789-93.
[10] Khanwalkar AR, Rathor A, Read AK, Paknezhad H, Ma Y, Hwang PH. Randomized, controlled, double-blinded clinical trial of effect of bevacizumab injection in management of epistaxis in hereditary hemorrhagic telangiectasia patients undergoing surgical cauterization. *Int Forum Allergy Rhinol.* 2022; 19, alr.22961.
[11] Morgan DJ, Kellerman R. Epistaxis: evaluation and treatment. *Prim Care*. 2014; 41 (1), 63-73.
[12] Sabbà C, Pasculli G, Suppressa P, et al. Life expectancy in patients with hereditary haemorrhagic telangiectasia. *QJM*. 2006; 99 (5), 327-34.
[13] de Gussem EM, Edwards CP, Hosman AE, et al. Life expextancy of parents with Hereditary Haemorrhagic Telangiectasia. *Orphanet J Rare Dis*. 2016; 11, 46.
[14] de Gussem EM, Kroon S, Hosman AE, et al. Hereditary Hemorrhagic Telangiectasia (HHT) and Survival: The Importance of Systematic Screening and Treatment in HHT Centers of Excellence. *J Clin Med Res*. 2020; 9 (11). doi: 10.3390/jcm9113581
[15] Shovlin CL, Sodhi V, McCarthy A, et al. Estimates of maternal risks of pregnancy for women with hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): suggested approach for obstetric services. *BJOG*. 2008; 115 (9), 1108-15.
[16] Dakeishi M, Shioya T, Wada Y, et al. Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. *Hum Mutat*. 2002; 19 (2), 140-8.
[17] Arai N, Akiyama T. A questionnaire-based survey to evaluate and improve the current HHT medical and social condition in Japan. *Surg Neurol Int*. 2020; 11 (323), 323.