



CLINICOPATHOLOGIC CONFERENCE

A Four-Year-Old Child With Digital Clubbing

Katherine Schultz,  Allison Divanovic, Christopher Towe, Alexander Miethke, Katie Wusik, Adrienne Hammill, and Hermine Brunner 

CASE PRESENTATION

Chief symptoms

A four-year-old female presented to our pediatric rheumatology clinic with the chief symptom of periodic fevers and abdominal pain.

History of the present illness

The patient's fevers began 4 months prior to presentation following a documented streptococcal pharyngeal infection, with a maximum temperature of 104°F. They occurred every 1–2 weeks and would then last a duration of 4–6 hours. Fevers were followed by severe abdominal pain that prevented eating. She did not have associated emesis, diarrhea, or constipation.

Medical, family, and social history

The past medical history of the patient included allergic rhinitis, characterized by rhinorrhea and congestion, which was treated with nasal spray. Otherwise, she was reported to have normal growth and development. There was no known family history of autoimmunity, including inflammatory bowel disease, systemic lupus erythematosus, vasculitis, psoriasis, or Raynaud's syndrome. Social history was noncontributory. There were no known relevant environmental exposures.

Review of systems

Review of systems was notable for lack of joint pain or swelling, digital clubbing, myalgia, limp, rash, fatigue, or headaches. The patient's parents denied that she had experienced respiratory symptoms, including shortness of breath, dyspnea on exertion,

cough, or snoring. There was no history of recurrent respiratory infections.

Physical examination

The girl was a well-appearing child without dysmorphic features. Vital signs were normal, though pulse oximetry was not obtained initially. There were no oral lesions, the oropharynx was clear, and tonsils were without exudate. Findings of ophthalmic examination were normal. Cardiac examination did not reveal murmur, rub, gallop, extra heart sounds, or arrhythmia. Lung examination demonstrated normal and symmetric air entry bilaterally. Her abdomen was soft, nontender to palpation, and without hepatosplenomegaly. Musculoskeletal examination was notable for redness overlying the distal interphalangeal joints and bilateral finger and toe clubbing (Figure 1). There was no evidence of synovitis or muscle tenderness or weakness. The patient had a normal gait without evidence of limp.

Laboratory evaluation

Results of initial laboratory tests were notable for an elevated level of alkaline phosphatase at 1,059 units/liter, but otherwise normal for transaminases, complete metabolic panel (albumin level of 6.5 gm/dl and bilirubin level 0.6 mg/dl), complete blood cell count, sedimentation rate, S100A8/S100A9, S100A12, complement levels, immunoglobulin levels, and C-reactive protein level (obtained between fever episodes). Antinuclear antibodies were negative.

Radiologic evaluation

A chest radiograph demonstrated nonspecific peribronchial thickening.

Katherine Schultz, MD, Allison Divanovic, MD, Christopher Towe, MD, Alexander Miethke, MD, Katie Wusik, LGC, Adrienne Hammill, MD, Hermine Brunner, MD, MSc, MBA: Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to Katherine Schultz, MD, Division of Rheumatology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229. Email: kjschult08@gmail.com.

Submitted for publication October 22, 2019; accepted in revised form August 13, 2020.



Figure 1. An example of clubbing on a child's hand, with notable redness over the distal phalanges. Photo courtesy of Dr. Grant Schuler (Cincinnati Children's Hospital Medical Center).

CASE SUMMARY

The patient is a 4-year-old female child with a family-reported history of recurrent fevers and associated abdominal pain who was found to have digital clubbing on physical examination.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of clubbing and of recurrent fevers are broad. This review will cover the differential of clubbing, particularly in the setting of recurrent fever.

The exact mechanism behind clubbing remains controversial, though several theories have been proposed (1). One such theory suggests that increased serum concentrations of growth hormone are associated with clubbing, although that has not been demonstrated in all cases of patients with clubbing. It has also been proposed that local vascular changes lead to arteriovenous anastomoses that result in changes of digital microcirculation, though firm evidence in support of this theory is lacking. Another theory proposes that clubbing is a function of platelet production, wherein the normal process of megakaryocyte breakdown into platelets inside the lungs is disrupted, allowing whole megakaryocytes to circulate. The megakaryocytes then become trapped in the finger or toe tip circulation. There, the megakaryocytes release platelet-derived growth factor, ultimately leading to the growth of vascular smooth muscle cells and fibroblasts. However, this theory does not

explain the existence of clubbing in all disease entities (1). Thus, the exact pathophysiologic process of clubbing remains unknown.

Despite the pathophysiology being uncertain, clubbing is a definite sign of pathologic changes, and the differential diagnosis includes primary and secondary causes. Primary clubbing can be seen in primary hypertrophic osteoarthropathy (PHO) (2). PHO is also known as pachydermoperiostosis, a rare genetic syndrome affecting the skin and bones. It is characterized by digital clubbing, periosteal new bone formation, coarse facial features, and skin thickening. It typically arises either during the first year of life or during puberty (3). Causes of secondary clubbing are more diverse, as detailed below (Table 1). Causes of secondary clubbing with associated fever are also delineated.

Pulmonary involvement. The presence of clubbing raises concern for pulmonary involvement. This includes underlying pulmonary disease such as cystic fibrosis, pulmonary arteriovenous malformations (AVMs [1]), or causes of diffuse lung disease. Diffuse lung disease is further characterized as being either intrinsic lung disease (e.g., idiopathic interstitial pneumonia, aspiration syndromes), associated with systemic disease (e.g., connective tissue diseases, metabolic storage diseases), or found in infancy (e.g., due to inborn errors of surfactant metabolism) (4).

Our patient was Caucasian, which could raise suspicion for cystic fibrosis, a condition more common in this racial group.

Table 1. Differential diagnoses for digital clubbing*

Pulmonary
Cystic fibrosis†
Diffuse lung disease
Hypersensitivity pneumonitis†
Pulmonary arteriovascular malformation
Hepatopulmonary syndrome
Cardiac
Cyanotic heart disease
Multisystem
COPA syndrome
Sarcoidosis†
CINCA syndrome†
POEMS syndrome†
Gastrointestinal
Inflammatory bowel disease†
Liver disease
Celiac sprue
Juvenile polyposis coli
Neoplastic
Bronchogenic carcinoma†
Pleural tumor†
Lymphoma†
Nasopharyngeal carcinoma†
Mesothelioma†
Infectious disease
Tuberculosis†
Infective endocarditis†
Chronic parasite infection†
HIV†
Vascular
Venous stasis
Psychiatric
Laxative abuse

* Adapted from Spicknall et al (1). CINCA = chronic infantile neurologic cutaneous articular syndrome; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin abnormalities.

† Diagnoses that can be associated with fever.

However, she lacked other signs to suggest cystic fibrosis, such as thick or sticky stools or poor growth. Results on a sweat chloride test were indeterminate, but CFTR gene sequencing did not support the presence of a pathologic mutation.

Pulmonary AVMs can result in digital clubbing (1). Such AVMs can be the result of direct communication between the pulmonary arteries and pulmonary veins. This is most often due to congenital malformations (5). Sometimes, pulmonary AVMs can be acquired, such as in hereditary hemorrhagic telangiectasia (HHT, also known as Rendu-Osler-Weber syndrome) (5,6). They may also be acquired in trauma, metastatic carcinoma, or infections (5).

Lastly, diffuse lung disease was excluded as a computed tomography (CT) scan of the chest did not show parenchymal lung disease.

Cardiac involvement. Cyanotic heart lesions have been associated with clubbing (1,7,8). For example, there is a case report of a child with unilateral finger clubbing. This child was ultimately found to have an absent aortic arch and was relying

on a patent ductus arteriosus for blood supply (7). There is also evidence in the literature of patent ductus arteriosus being associated with PHO (8). While PHO is considered a primary cause of clubbing, it is worth mentioning here that clubbing as the finding of a patent ductus arteriosus should not reassure the clinician that another entity, such as PHO, is not involved. These conditions are not associated with fever, however, lowering our initial suspicion for a primary cardiac cause in this patient. Additionally, her chest radiographic was not concerning for cardiomegaly.

Rheumatic diseases. With the presentation of fevers and noted clubbing, concern arose for the possibility of systemic juvenile idiopathic arthritis (JIA) complicated by lung disease, also known as diffuse parenchymal lung disease (9,10). There is increasing awareness of lung disease in systemic JIA. Though some have suggested the involvement of uncontrolled systemic JIA activity or medication exposure as the cause of the increasing rates of systemic JIA-associated lung disease, the exact immunopathologic cause remains unknown. It was recently reported that up to 78% of patients with systemic JIA and lung disease have clubbing (10). Again, these patients are also notably symptomatic with shortness of breath, cough, and/or chest pain (10,11). Our patient did not exhibit pulmonary symptoms, but systemic JIA with interstitial lung disease (ILD) remained on our differential.

When considering periodic fevers, another rheumatic condition to consider is chronic infantile neurologic, cutaneous, articular (CINCA) syndrome, also known as neonatal-onset multisystem inflammatory disease (NOMID) (12). This is a rare autoinflammatory condition characterized by mutation in the *FCAS1* gene and is within the spectrum of other periodic fever syndromes. Historically, CINCA/NOMID has been characterized by neonatal onset (or young infancy onset) of persistent rash, optic disc changes, and progressive neurologic involvement. There have been cases of older children who have clubbing associated with this condition (12). Our patient lacked a rash, and eye or neurologic involvement, to suggest CINCA/NOMID.

Another disease with increasing recognition is COPA syndrome, an autosomal dominant autoinflammatory condition named for mutations in the *COPA* gene (13). COPA syndrome is characterized by restrictive lung disease, arthritis (14), and renal disease (13). Patients with COPA syndrome frequently have clubbing due to their underlying restrictive lung disease (14,15). COPA syndrome is a relatively new and rare disorder, and the incidence and prevalence of this condition are still uncertain. Recurrent or periodic fever does not appear to be a defining feature of COPA syndrome (14,15). This lowered our suspicion that COPA syndrome was the cause of our patient's presentation. She also did not have arthritis or renal involvement to support this diagnosis.

Interestingly, there is a case report of a child with recurrent fevers and hepatosplenomegaly who ultimately developed

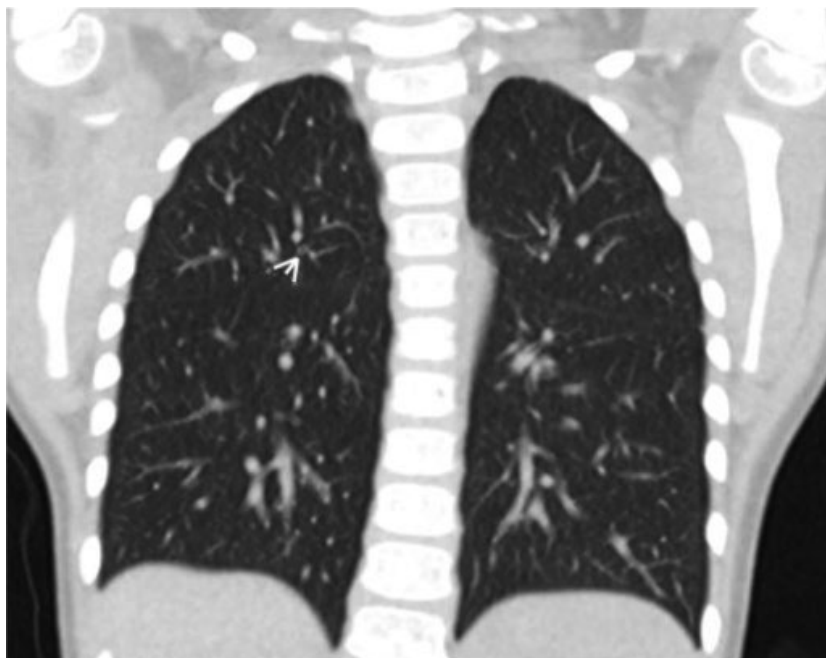


Figure 2. Computed tomography scan of the patient's chest without contrast. There was diffuse but mild nonspecific peribronchovascular thickening, with one such area of peribronchovascular thickening highlighted (**arrow**). There was no evidence of interstitial lung disease.

clubbing secondary to portal hypertension due to Takayasu arteritis (16). Given the report of fevers and the initially elevated level of alkaline phosphatase, systemic sarcoidosis was considered. Sarcoidosis is a condition characterized by necrotizing granuloma formation in multiple tissues with manifestations dependent on the organ (17). Our patient did not have lymphadenopathy, parenchymal lung disease, organomegaly, or hypercalcemia that would suggest this diagnosis, and the elevated alkaline phosphatase level normalized spontaneously, further lowering suspicion for this disease.

Gastrointestinal (GI) conditions. GI-related causes of clubbing include inflammatory bowel disease, juvenile polyposis, hepatic disorders (1,18), and celiac disease (1). Though our patient had abdominal pain following fevers, she did not have diarrhea, constipation, mucosal sores, or other findings to suggest primary GI disease. Her initially elevated alkaline phosphatase finding normalized without intervention, also lowering our suspicion for primary GI disease.

Neoplastic disease. Clubbing has been associated with neoplasms for decades, particularly with pulmonary neoplasms (19). However, for our patient, a primary pulmonary neoplasm was felt to be unlikely given her age and lack of risk factors, such as smoking or exposure to smoke. She also lacked systemic symptoms, such as night sweats, coughing, or weight loss, to suggest neoplasm. Her chest radiograph did not demonstrate a mass that would be consistent with primary pulmonary neoplasm.

Infectious disease. Infectious causes of clubbing include more indolent infections, such as tuberculosis, infective endocarditis, HIV, or chronic parasitic infection (1). She lacked risk factors for these infections, lowering suspicion that they were the cause of her symptoms.

CLINICAL COURSE

The patient's fevers resolved without intervention within months of her initial consult visit with rheumatology. It was later discovered she had had dental procedures completed prior to her episodes. It was thought that perhaps some bacterial seeding had contributed to her fevers.

The patient was referred to pulmonology for further evaluation of clubbing noted in the setting of peribronchovascular thickening seen on chest radiograph. Pulmonology evaluation revealed that pulse oximetry was 97% on room air. She had a normal 6-minute walk test. Chest CT also demonstrated peribronchovascular thickening but no other abnormality (Figure 2). As a result, a contrast echocardiogram was performed. The echocardiogram showed normal cardiac anatomy and function. It also demonstrated 20–30 bubbles in the left atrium within 4 beats following injection of bubbles into the right heart. This was felt to be concerning for pulmonary arteriovenous malformation (AVM) (Figure 3). She was then referred to cardiology and gastroenterology and evaluated by our GI team due to an elevated level of alkaline phosphatase, though this finding normalized without intervention, and the cause of the original elevation was not determined. Results from a Doppler ultrasound of the patient's liver were normal.

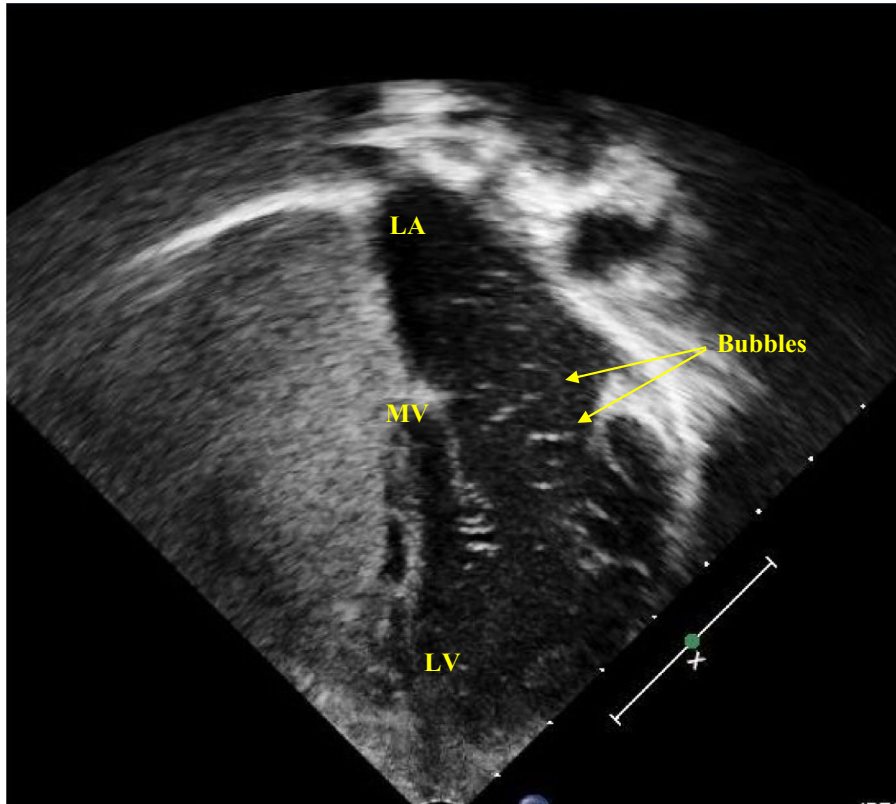


Figure 3. Echocardiogram with contrast demonstrating 20–30 bubbles in the left atrium (**arrows**) within 4 heart beats following injection of bubbles into the right side of the heart. Cardiac anatomy and function were normal. LA = left atrium; LV = left ventricle; MV = mitral valve. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24428/abstract>.

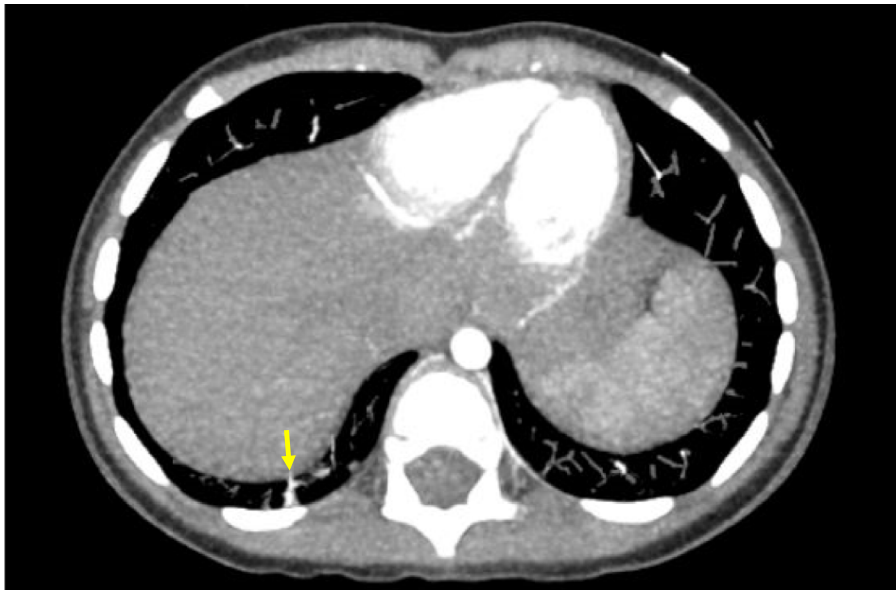


Figure 4. Computed tomography angiogram of the patient's chest in the axial plane. There was evidence of multiple small pulmonary arteriovenous malformations. These are found at the posterior aspects of the bilateral lower lung lobes. They are characterized by enhancement, representing feeding arteries and draining veins. The largest pulmonary arteriovenous malformation is highlighted (**arrow**). Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24428/abstract>.

Table 2. Curaçao Criteria for diagnosing hemorrhagic hereditary telangiectasia*

Epistaxis
Spontaneous, recurrent nose bleeds
Telangiectasias
Multiple
At characteristic sites: lips, oral cavity, fingers, and nose
Visceral lesions
Gastrointestinal telangiectasia, pulmonary AVM, hepatic AVM, cerebral AVM, and spinal AVM
Family history
First-degree relative with HHT

* Diagnosis is definite if 3 criteria are present, possible or suspected if 2 criteria are present, or unlikely if fewer than 2 criteria are present. Adapted from Shovlin et al (6). AVM = arteriovenous malformation; HHT = hereditary hemorrhagic telangiectasia.

Eventually she was referred to the Cincinnati HHT Center of Excellence for evaluation and management of HHT. It was then noted at the Center that she had 3 skin telangiectasias, found on the right wrist, right cheek, and left wrist. A subsequent CT angiogram of the chest demonstrated multiple small pulmonary AVMs at the lung bases (Figure 4). A magnetic resonance imaging (MRI) scan of the brain was normal. Genetic testing for HHT—endoglin gene (*ENG*), activin A receptor type II-like 1 gene (*ACVRL1*), mothers against DPP homolog 4 (*SMAD4*), growth differentiation factor 2 (*GDF2*) (20), ephrin type-B receptor 4 (*EPHB4*) (21), and Ras p21 protein activator (*RASA1*) (22)—was completed by a laboratory and returned with negative results for these genes. There was no family history consistent with HHT. Mother and father denied any history of recurrent nosebleeds. While most cases of HHT are autosomal dominant as mentioned above, there are de novo cases reported (23). There is also an increasing amount of data supporting that the first patient with HHT in a family may be mosaic, and therefore show a negative result on blood testing for HHT (24,25). The patient did ultimately meet clinical diagnostic criteria for possible HHT under the Curaçao Criteria (6), the recommended criteria used for clinical diagnosis of HHT (Table 2).

The patient is currently asymptomatic and being monitored in the Cincinnati HHT Center of Excellence every 6 months. This Center is a multidisciplinary clinic, with the core specialties involved including a hematologist, a genetic counselor, interventional radiology, and an ear, nose, and throat surgeon. Our Center also includes a pulmonologist, a cardiologist, a gastroenterologist, a neurologist, a neuroradiologist, a neurosurgeon, and a plastic surgeon (26). As part of her monitoring, she will require several clinical tests per international guidelines (27). She will need a repeat brain MRI upon entering adulthood, as brain AVMs can grow with puberty. She will require repeat bubble echocardiograms every 2–3 years to monitor the state of her existing pulmonary AVMs and evaluate for anticipated complications, such as the risk of embolic and/or infectious events. She will require testing of annual hemoglobin levels starting at age 35 years due to risk for internal bleeding from

AVMs (especially GI AVMs), as well as annual liver screening with liver function testing. She will also need routine colonoscopy at age 50 years, or sooner if she has evidence of GI bleed (27). Finally, she will also require antibiotic prophylaxis due to the risk for infectious emboli secondary to her existing pulmonary AVMs.

DISCUSSION

Hereditary hemorrhagic telangiectasia is an autosomal dominant disease characterized by vascular dysplasia (28). Mutations in several genes—*ENG*, *ACVRL1*, *MADH4*, *SMAD*, *GDF2*, *RASA1* (20), *EPHB4* (21), *RASA1* (22)—have been associated with HHT, all of which affect proteins in the transforming growth factor β (TGF β) superfamily (20,28). Unfortunately, a subset of patients and families (15–20%) with HHT do not have an identifiable mutation known to cause HHT (28). The majority of patients who do have a known genetic mutation will have one in the *ENG* or *ACVRL1* genes (28).

The vascular abnormalities that characterize HHT can occur in any organ, with large vessel involvement affecting the liver, lung, and brain (in descending order) and small vessel involvement affecting the nasal mucosa, GI tract, and skin (29). Patients classically present with a triad of epistaxis, telangiectasias, and a family history of HHT (6). However, in reality, patients can present in a myriad of ways, none of which are pathognomonic for the disease (29). Additionally, diagnosis in childhood is complicated because the Curaçao Criteria (Table 2) have been shown to have poor sensitivity and specificity in children who are less than 15 years old (30). More concerning, patients with vascular malformations may remain asymptomatic until the development of a catastrophic event urges them to receive medical attention (29).

Our patient only had a few scattered telangiectasias. These were noted only after very careful examination and imaging suggestive of telangiectasias had been obtained. The most important diagnostic clue in evaluating this patient was her presentation with digital clubbing, which was due to her pulmonary AVMs (29).

Pulmonary AVMs are quite common in HHT, affecting up to 50% of patients throughout their lifetime (28). Moreover, of all cases of pulmonary AVMs, 80–90% are due to an underlying diagnosis of HHT (28). The data are sparse on sporadic pulmonary AVMs, and according to our experts, occurrence of pulmonary AVMs outside of HHT is rare unless it occurs with severe pulmonary, liver, or cardiac disease, which our patient lacked.

The diagnosis of pulmonary AVMs is of particular importance. The direct connection between arterial and venous blood supply leaves the patient vulnerable to paradoxical emboli that can cause cerebral abscess or stroke (28). Treatment is aimed at embolization of the malformation (28). Other

risks associated with pulmonary AVMs include rupture, leading to massive blood loss (28). Therefore, any patient suspected of having HHT should be screened with a bubble contrast echocardiogram (31).

Hepatic AVMs are even more common in HHT, with up to 75% of patients being affected, though not all patients experience symptoms (31). When patients do experience symptoms, most present with heart failure, portal hypertension, or biliary disease. These symptoms can be managed medically (31), though liver transplantation is favored in Europe and has demonstrated good outcomes (32). Until recently, initial or routine screening for hepatic AVMs if asymptomatic (lacking a bruit and with normal transaminases) was not routinely recommended in HHT patients (31). Our institution recommends checking liver function tests, including gamma glutamyl transferase and brain natriuretic peptide, annually.

For rheumatologists, HHT is important as it can mimic the skin findings of limited systemic sclerosis (SSc) (formerly the CREST variant of scleroderma). Limited SSc is characterized by calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, and telangiectasia. This was not in our initial diagnosis but is worth mentioning here as skin findings can precede other findings by years (33). It has been suggested that anticentromere antibodies can distinguish limited SSc from HHT (33). However, there are case reports where this is not the circumstance and distinguishing between limited SSc and HHT may present a diagnostic dilemma (34).

There have been reports of other diseases associated with HHT. An example is juvenile polyposis HHT (JP-HHT) (31,35), an autosomal dominant disorder characterized by gastrointestinal polyps and increased risk for GI cancer (35). These patients require further screening with colonoscopy and endoscopy every 1–2 years beginning with first symptom or at age 12 years, whichever comes first (31).

Interestingly, patients with JP-HHT have a known genetic variation in the *SMAD4* gene (35,36). *SMAD4* encodes a protein in the TGF β pathway (36). This is relevant, as there is also a case report of a patient with systemic JIA and JP-HHT with a known variation in the *SMAD4* gene (36). Though our patient ultimately did not have persistent fevers or blood work supporting a diagnosis of systemic JIA, this association may be important for rheumatologists who have patients presenting with fevers, clubbing, and findings of telangiectasias.

FINAL DIAGNOSIS

Hereditary hemorrhagic telangiectasia.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version

to be submitted for publication. Dr. Schultz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Schultz, Divanovic, Towe, Miethke, Wusik, Hammill, Brunner.

Acquisition of data. Schultz, Divanovic, Towe, Miethke, Wusik, Hammill, Brunner.

Analysis and interpretation of data. Schultz, Divanovic, Towe, Miethke, Wusik, Hammill, Brunner.

REFERENCES

- Spicknall KE, Zirwas MJ, English JC III. Clubbing: an update on diagnosis, differential diagnosis, pathophysiology, and clinical relevance. *J Am Acad Dermatol* 2005;52:1020–8.
- Jyotsna M, Tharakan J. Clinical Sign: clubbing. *Indian J Cardiovasc Dis Women WINCARS* 2017;02:e1–9.
- Zhang Z, Zhang C, Zhang Z. Primary hypertrophic osteoarthropathy: an update. *Front Med China* 2013;7:60–4.
- Vece TJ, Fan LL. Diagnosis and management of diffuse lung disease in children. *Paediatr Respir Rev* 2011;12:238–42.
- Khurshid I, Downie GH. Pulmonary arteriovenous malformation. *Postgrad Med J* 2002;78:191–7.
- Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000;91:66–7.
- Dorney ER, Fowler NO, Mannix EP. Unilateral clubbing of the fingers due to absence of the aortic arch. *Am J Med* 1955;18:150–4.
- Levin SE, Harrisberg JR, Govendrageloo K. Familial primary hypertrophic osteoarthropathy in association with congenital cardiac disease. *Cardiol Young* 2002;12:304–7.
- Van Manen MJ, Vermeer LC, Moor CC, Vrijenhoef R, Grutters JC, Veltkamp M, et al. Clubbing in patients with fibrotic interstitial lung diseases. *Respir Med* 2017;132:226–31.
- Schulert GS, Yasin S, Carey B, Chalk C, Do T, Schapiro AH, et al. Systemic juvenile idiopathic arthritis-associated lung disease: characterization and risk factors. *Arthritis Rheumatol* 2019;71:1943–54.
- Kimura Y, Weiss JE, Haroldson KL, Lee T, Punaro M, Oliveira S, et al. Pulmonary hypertension and other potentially fatal pulmonary complications in systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)* 2013;65:745–52.
- Indian Pediatrics*. CINCA syndrome. URL: <http://www.indianpediatrics.net/dec2007/dec-933-936.htm>.
- Vece TJ, Watkin LB, Nicholas SK, Canter D, Braun MC, Guillerman RP, et al. Copa syndrome: a novel autosomal dominant immune dysregulatory disease. *J Clin Immunol* 2016;36:377–87.
- Noorelahi R, Perez G, Otero HJ. Imaging findings of Copa syndrome in a 12-year-old boy. *Pediatr Radiol* 2018;48:279–82.
- Brennan M, McDougall C, Walsh J, Crow Y, Davidson J. Copa mutation—a new condition to consider with polyarthritis and interstitial lung disease [case report G426]. *Arc Dis Child* 2017;102:A167–8.
- Herrera CN, Tomala-Haz JE. Portal hypertension: an uncommon clinical manifestation of Takayasu arteritis in a 9-year-old child. *Open Access Rheumatol* 2016;8:115–8.
- Yancey J, Luxford W, Sharma OP. Clubbing of the fingers in sarcoidosis. *JAMA* 1972;222:582.
- McPhee SJ. Clubbing. In: *Clinical methods: the history, physical, and laboratory examinations*. Boston: Butterworths; 1990. URL: <http://www.ncbi.nlm.nih.gov/pubmed/21250207>.
- Craig JW. Hypertrophic pulmonary osteoarthropathy as first symptom of neoplasm. *Br Med J* 1937;1:750–2.

20. McDonald J, Wooderchak-Donahue W, VanSant Webb C, Whitehead K, Stevenson DA, Bayrak-Toydemir P. Hereditary hemorrhagic telangiectasia: genetics and molecular diagnostics in a new era. *Front Genet* 2015;6:1.
21. Wooderchak-Donahue WL, Akay G, Whitehead K, Briggs E, Stevenson DA, O'Fallon B, et al. Phenotype of CM-AVM2 caused by variants in EPHB4: how much overlap with hereditary hemorrhagic telangiectasia (HHT)? *Genet Med* 2019;21:2007–14.
22. Wooderchak-Donahue W, Stevenson DA, McDonald J, Grimmer JF, Gedge F, Bayrak-Toydemir P. RASA1 analysis: Clinical and molecular findings in a series of consecutive cases. *Eur J Med Genet* 2012;55:91–5.
23. Gedge F, McDonald J, Phansalkar A, Chou LS, Calderon F, Mao R, Lyon E, et al. Clinical and analytical sensitivities in hereditary hemorrhagic telangiectasia testing and a report of de novo mutations. *J Mol Diagn* 2007;9:258–65.
24. Tørring PM, Kjeldsen AD, Ousager LB, Brusgaard K. ENG mutational mosaicism in a family with hereditary hemorrhagic telangiectasia. *Mol Genet Genomic Med* 2018;6:121–5.
25. McDonald J, Wooderchak-Donahue WL, Henderson K, Paul E, Morris A, Bayrak-Toydemir P. Tissue-specific mosaicism in hereditary hemorrhagic telangiectasia: implications for genetic testing in families. *Am J Med Genet A* 2018;176:1618–21.
26. Cincinnati Children's Hospital Medical Center. HHT Center of Excellence. URL: <https://directory.curehht.org/hospital/cincinnati-childrens-hospital-medical-center>.
27. CureHHT. HHT International Clinical Guidelines. URL: <https://curehht.org/resource/hht-international-clinical-guidelines/>.
28. Kühnel T, Wirsching K, Wohlgemuth W, Chavan A, Evert K, Vielsmeier V. Hereditary hemorrhagic telangiectasia. *Otolaryngol Clin North Am* 2018;51:237–54.
29. Sabba C, Gallitelli M, Pasculli G, Suppressa P, Resta F, Tafaro E. HHT: A rare disease with a broad spectrum of clinical aspects. *Curr Pharm Des* 2006;12:1217–20.
30. Pahl KS, Choudhury A, Wusik K, et al. Applicability of the Curaçao Criteria for the diagnosis of hereditary hemorrhagic telangiectasia in the pediatric population. *J Pediatr* 2018;197:207–13.
31. Kroon S, Snijder RJ, Faughnan ME, Mager HJ. Systematic screening in hereditary hemorrhagic telangiectasia. *Curr Opin Pulm Med* 2018;24:260–8.
32. Lerut J, Orlando G, Adam R, et al. Liver transplantation for hereditary hemorrhagic telangiectasia: report of the European liver transplant registry. *Ann Surg* 2006;244:854–64.
33. Fritzler MJ, Arlette JP, Behm AR, Kinsella TD. Hereditary hemorrhagic telangiectasia versus CREST syndrome: can serology aid diagnosis? *J Am Acad Dermatol* 1984;10:192–6.
34. Lee JB, Ben-Aviv D, Covello SP. The diagnostic quandary of hereditary haemorrhagic telangiectasia vs. CREST syndrome. *Br J Dermatol* 2001;145:646–9.
35. Gallione C, Aylsworth AS, Beis J, Berk T, Bernhardt B, Clark RD, et al. Overlapping spectra of SMAD4 mutations in juvenile polyposis (JP) and JP-HHT syndrome. *Am J Med Genet* 2010;152A:333–9.
36. Bishop J, Britton J, Murphy A, et al. Juvenile idiopathic arthritis associated with combined JP-HHT Syndrome: a novel phenotype associated with a novel variant in SMAD4. *J Pediatr Genet* 2018;07:78–82.