Digital Clubbing in Hereditary Hemorrhagic Telangiectasia/Juvenile Polyposis Syndrome

Hereditary hemorrhagic telangiectasia (HHT) (Osler-Weber-Rendu Syndrome) is a rare autosomal dominant vascular disorder characterized by the presence of multiple arteriovenous malformations (AVMs) and recurrent bleeding episodes. The diagnosis is based on the Curacao criteria: (i) spontaneous recurrent epistaxis, (ii) mucocutaneous telangiectasia, (iii) AVMs of visceral organs, and (iv) first degree relatives with a similar condition (1). Due to a common genetic pathway and SMAD4 gene mutation, juvenile polyposis syndrome (JPS) may coexist with HHT (2). The disease burden is high in overlapping HHT/JPS, but digital clubbing may be the only physical finding. Continuous meticulous management may improve the quality of life and reduce the risk of complications.

In 2000, a 15-year-old female patient was diagnosed with HHT based on epistaxis, multiple pulmonary AVMs, and a father who had similar symptoms. Other visceral AVMs were excluded. No telangiectasia was noted. On several occasions, pulmonary AVMs were managed with coil embolization (Figure 1), which successfully led to the resolution of dyspnea and cyanosis. Recurrent gastrointestinal bleedings led to severe transfusion-dependent anemia. Multiple polyps in the stomach, small intestine, and colon were repeatedly endoscopically removed, confirming the coexisting JPS. Genetic testing was not performed. Proctocolectomy was performed to prevent malignant transformation in the digestive tract.

Telangiectasias are the dermatological hallmark of the HHT and occur in up to 90% of patients with the typical onset in childhood, becoming more apparent with increasing age. They are most frequently found on the face, with highest incidence on the nose, lips, tongue, and ears, followed by the fingertips, trunk, and feet; telangiectasia is recognized as the most common of the three criteria required for the diagnosis of HHT (1). Interestingly, no cutaneous telangiectasia developed in our patient during years of follow-up. However, pulmonary AVMs led to digital clubbing of her both fingers and toes (Figure 2).

Digital clubbing is the focal enlargement of the connective tissue in the terminal phalanges, consequently changing the shape of nails, which become abnormally curved and shiny. It is associated with various infectious, neoplastic, inflammatory, and vascular conditions (3). Despite its well-known prevalence in certain conditions, the pathogenesis of this phenomenon remains elusive. Vascular, neural, and hormonal mechanisms have been considered, implicating the role of a wide range of substances, such as prostaglandins, bradykinin, estrogen, platelet-derived growth factor, hepatocyte growth factor, and growth hormone, however, none of these mechanisms provide a unifying explanation (4,5).

In digital clubbing, the increased vascularity in the nail-bed leads to hyperplasia of fibrous tissue and

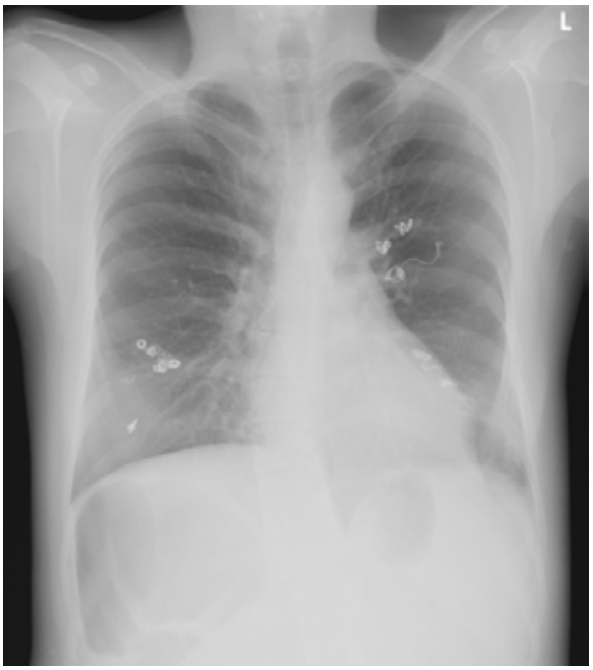

Figure 1. Chest X-ray showing multiple coils in both lungs 20 years after the embolization of pulmonary arteriovenous malformations.

Figure 2. Clubbing of fingers and toes in hereditary hemorrhagic telangiectasia/juvenile polyposis syndrome 20 years after coil embolization of pulmonary arteriovenous malformations.

edema, resulting in a loss of the hyponychial angle, fluctuance of the nail-bed, and an abnormal phalangeal depth ratio (5). The clinical assessment of the clubbing is based on the measurement of the distal phalangeal depth (DPD) of the finger (at the nail base) and the interphalangeal depth (IPD). A DPD/IPD ratio >1 is defined as clubbing, while a DPD/IPD ratio <1 is defined as normal (3).

Clubbing is a potentially reversible phenomenon provided that the underlying condition is cured (4,5). In the context of pulmonary AVMs, abnormal communication between the pulmonary artery and pulmonary vein outside the capillary bed leads to right-to-left shunt physiology that clinically presents as dyspnea, cyanosis, and clubbing. Embolization of AVMs as the first-line therapy resolved systemic symptoms in our patient, and therefore no other treatment options were pulmonary considered further. However, 20 years later, despite the treatment, the severe clubbing of her both fingers and toes remained (Figure 2).

Based on our findings, HHT should be considered in differential diagnosis of patients with digital clubbing resulting from AVMs, in particular when no skin telangiectasia is present.

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