A 66-year-old man presented to his cardiologist with a 3-month history of feeling tired, a 6.8 Kg weight loss, and occasional night sweats. He had a remote 17–pack-year history of smoking. Eighteen months previously, he had undergone an aortic valve replacement for symptomatic aortic valve stenosis. His examination revealed a normal temperature, a heart rate of 95 bpm, a blood pressure of 140/90 mm Hg, a soft aortic ejection flow murmur without a detectable diastolic murmur, and no clinical evidence of heart failure. He was noted to have painless bilateral finger clubbing without evidence of palpable splenomegaly or peripheral embolic phenomena. His optic fundi were normal. In addition to the history of weight loss, fatigue, and occasional night sweats, the presence of finger clubbing leads one to consider its major causes.1

Digital clubbing was first described by Hippocrates in 400 bc in a patient with empyema. This unique examination finding can provide an immediate clue that a serious underlying condition may exist. In 1938, Lovibond2 described the “profile” sign (Figure),3 which, if >180°, indicates true clubbing of the fingers. (The normal angle between the nail bed and the proximal nail fold is 160°.) In addition, there is periungual edema and a softening of the nail bed.2 Digital clubbing may occur alone or can be part of a syndrome of joint pain and swelling associated with periostosis of tubular bones (hypertrophic osteoarthropathy [HOA]). In 1944, Paul Dudley White said,

Clubbing of the fingers and toes associated with cyanosis is found in certain congenital cardiovascular defects (the morbus caruleus). Clubbing without cyanosis is found in subacute bacterial endocarditis. However, it must be remembered that clubbed fingers are often found with noncardiac conditions, most commonly of all in pulmonary diseases; even ulcerative colitis may be the underlying cause, and a familial type of unknown etiology has been described.4

These comments reflect the spectrum of disease of his time.

The major causes to consider include the following:

1. Pulmonary malignancy. Primary lung cancer, lymphoma, pleural mesothelioma, and secondary pulmonary malignancies can all be accompanied by clubbing. Primary lung and pleural tumors may also exhibit pulmonary HOA. In 1956, Flavell5 described 5 patients with pulmonary malignancies (some inoperable) and significant, at times incapacitating, pain and swelling of the wrists, elbows, knees, or ankles that was relieved within hours or weeks by division of the vagus nerve. Tumor resection can also abate or abolish both clubbing and the associated painful osteoarthropathy. More recently, video-assisted left truncal vagotomy provided relief within hours to a patient with inoperable lung cancer who had suffered incapacitating joint symptoms.6 Painful clubbing is more likely in patients with bronchogenic carcinoma, lung abscess, and bronchiectasis.7

2. Chronic infection (or inflammation). Digital clubbing has classically been associated with chronic infections such as bronchiectasis, lung abscess, empyema, pulmonary tuberculosis, and infective endocarditis.8 Both inflammatory bowel disease (Crohn disease more than ulcerative colitis) and chronic liver disease have been associated with clubbing. Furthermore, clubbing has been seen with HIV and chronic parasitic infections with Trichuris.
Clubbing is more prevalent with active inflammatory bowel disease, especially when macroscopic disease is confined to the area of the gut innervated by the vagus nerve (ie, the small and large intestine as far as the midtransverse colon). Mucosa with active disease shows higher spontaneous VEGF production than normal mucosa, and the expression of VEGF-A and its receptor, VEGFR-2, are increased in inflamed bowel. Thus, VEGF appears to be a promoter of angiogenesis and inflammation in bowel disease and, when overexpressed in a mouse colitis model, worsens the condition.

Most patients with end-stage chronic liver disease undergoing evaluation for transplantation have intrapulmonary shunts (especially those with Child-Pugh classification C), and they can have lower resting PaO₂ levels. Substantial right-to-left shunting in the lungs in association with cirrhosis, cyanosis, and clubbing was described by Rodman et al., who later documented minor degrees of arterial desaturation and increased venous admixture attributed to intrapulmonary shunting in cirrhotic patients. In patients with cirrhosis, there are increased numbers of small, dilated blood vessels in the alveolar walls (especially vessels <35 µm), with some vessels just beneath the pleural surface having the appearance of spider nevi. In rodent studies of cirrhosis, with the progression of fibrosis, there is hepatocellular hypoxia and increased expression of VEGF and VEGF receptors, which correlate with the density of new microvessels. After successful liver transplantation in a cirrhotic patient with cyanosis, clubbing, oxygen desaturation, and right-to-left shunting...
(demonstrated by perfusion scanning), all of these abnormalities resolved.33

In the pathogenesis of digital clubbing, local hypoxia, platelet activation, release of signal proteins such as VEGF, and stimulation of angiogenesis and other cellular activities are probably contributory.

In our patient, routine blood tests and blood cultures were unremarkable. An echocardiogram revealed a normally functioning aortic valve without evidence of vegetations, valve regurgitation, or abscess formation. A computed tomography of the chest revealed a lung tumor near the periphery of the lung. Fine-needle biopsy of the mass led to the diagnosis of adenocarcinoma. There was no evidence of lymphadenopathy. A lobectomy was performed. Within weeks, the finger clubbing disappeared. When new-onset digital clubbing is observed in the absence of overt pathology, a screening chest computed tomography seems warranted.

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Dr Samuel Goldhaber invited me to write this update when he heard my interest had been stimulated by self-diagnosed clubbing. The case history bears only a faint resemblance to my condition.

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Digital Clubbing
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