Digital Clubbing

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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), 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 periungal 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.1

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 plural tumors may also exhibit pulmonary HOA. In 1956, Flavell3 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.4 Painful clubbing is more likely in patients with bronchogenic carcinoma, lung abscess, and bronchiectasis.5

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.6 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.
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budding from the tips, and splayed affer-
the normally vertically oriented capillary
with plexus formation at right angles to
tive, abnormal capillary growth pattern,
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Figure. As demonstrated, the normal hyponychial angle is 160°, and an angle >180° is consistent with clubbing. Reprinted with permis-
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trichuria (whipworm) and schis-
tosomal colonic polypsis.
3. Cyanotic congenital heart disease.
4. Primary HOA. This is a rare familial
condition. Homozygous indi-
viduals have chronically elevated
prostaglandin E2 levels and promi-
nent clubbing. Mutations were first
reported in 2008 in the 15-hydroxy-
prostaglandin dehydrogenase (HPGD)
gene encoding the major
prostaglandin catabolizing enzyme
(prostaglandin E2).9 Heterozygotes
show milder manifestations. In
individuals with autosomal-re-
cessive primary HOA, a mutation
in the prostaglandin transporter
SLCO2A1 has been described.10,11
In patients with liver disease treated
with prostaglandins, clubbing and
cortical hyperostosis resembling
HOA developed and then reversed
when therapy was completed.12 In
patients with primary HOA, plas-
ma levels of vascular endothelial
growth factor (VEGF) are higher
than in control subjects.13

Pathophysiology
Knowledge of the pathophysiology of
clubbing is incomplete. The case report
of a 24-year-old woman with reversed
shunting through a patent ductus arterio-
sus and oxygen saturations >90% in her
arms and 63% in her femoral artery with
clubbing and cyanosis only of her toes
(and HOA of her lower extremities) sug-
gests that hypoxia plays a role.14 Patients
with acquired clubbing have a distinc-
tive, abnormal capillary growth pattern,
with plexus formation at right angles to
the normally vertically oriented capillary
loops, arborized loops with branches
budding from the tips, and splayed affer-
ent and efferent limbs of the capillary
loop.15 Platelet clusters aggregating in
the distal vasculature of the digits may
mediate the morphological changes of
clubbing.16 Furthermore, human mega-
karyocytes within bone marrow produce
and secrete VEGF in an inducible man-
ner. VEGF delivered to sites of vascular
injury by activated platelets may initi-
ate angiogenesis.17 In normal neonates,
plasma VEGF levels are elevated but
within 3 months fall rapidly. In cyanotic
children, VEGF levels remain elevated
and are inversely related to oxygen satu-
rati on,18 and the functional capacities of
circulating endothelial progenitor cells
(proliferation, migration, and adhesion)
are augmented.19

That resection of the vagus nerve
can abate or abolish both clubbing and
pulmonary osteoarthropathy led to the
theory that the vagus nerve may be a
key signaling pathway.20 In patients
with bronchogenic carcinoma and
unequivocal clubbing, both VEGF and
platelet-derived growth factor, which
are released with platelet aggrega-
tion and are hypoxically regulated,
are increased in the digits that contain
platelet clusters compared with control
subjects.21 In patients with lung cancer,
plasma levels of VEGF are signifi-
cantly higher than in control subjects,13
and VEGF is known to be a predomi-
nant angiogenic tumor growth factor.22
Removal of a pulmonary large-cell
adenocarcinoma in a female patient with
digital clubbing and primary
HOA dramatically reduced abnormally
high plasma and serum VEGF levels.
Her bone pain and clubbing deformi-
ties regressed and were absent a year
after surgery.23 The resected lung tumor
showed 45% greater VEGF mRNA
expression than normal lung.

Clubbing is more prevalent with
active inflammatory bowel disease,
especially when macroscopic disease
is confined to the area of the gut inner-
vated by the vagus nerve24 (ie, the small
and large intestine as far as the midtrans-
verse colon).25 Mucosa with active dis-
ease shows higher spontaneous VEGF
production than normal mucosa,26 and
the expression of VEGF-A and its
receptor, VEGFR-2, are increased in
inflamed bowel.27 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.27

Most patients with end-stage chronic
liver disease undergoing evaluation for
transplantation have intrapulmo-
nary shunts (especially those with
Child-Pugh classification C), and they
can have lower resting Pao2 levels.28
Substantial right-to-left shunting in the
lungs in association with cirrhosis, cya-
nosis, and clubbing was described by
Rodman et al,29 who later documented
minor degrees of arterial desaturation
and increased venous admixture attrib-
uted to intrapulmonary shunting in
cirrhotic patients.30 In patients with cir-
rhosis, there are increased numbers of
small, dilated blood vessels in the alveo-
lar walls (especially vessels <35 µm),
with some vessels just beneath the pleu-
ral surface having the appearance of spi-
der nevi.31 In rodent studies of cirrhosis,
with the progression of fibrosis, there is
hepatocellular hypoxia and increased
expression of VEGF and VEGF recep-
tors, which correlate with the density
of new microvessels.32 After successful
liver transplantation in a cirrhotic
patient with cyanosis, clubbing, oxygen
desaturation, and right-to-left shunting
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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 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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References
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