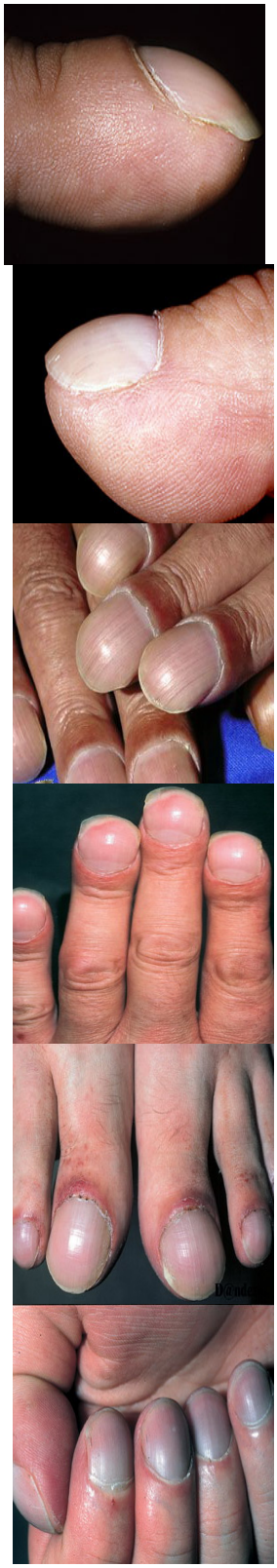

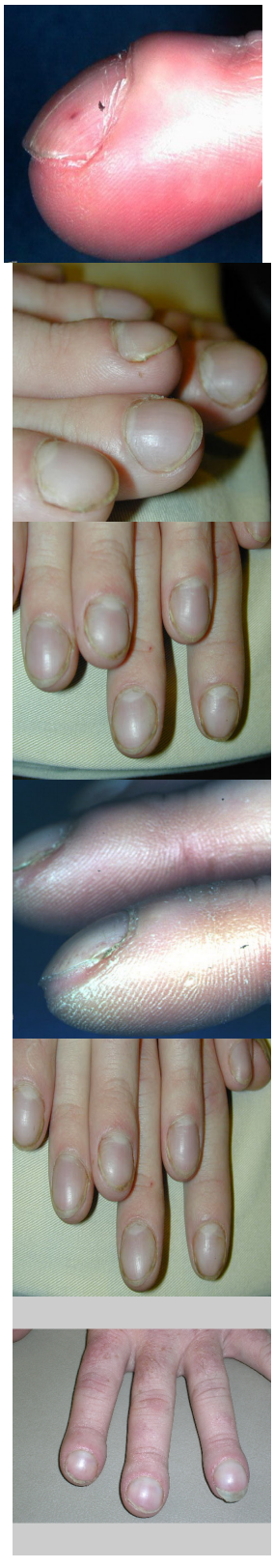

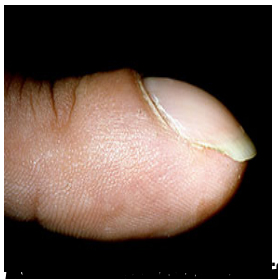

Pathophysiology

The specific pathophysiologic mechanism of digital clubbing remains unknown. Many theories have been proposed, yet none have received widespread acceptance as a comprehensive explanation for the phenomenon of digital clubbing. As stated best by Samuel West in 1897, "Clubbing is one of those phenomena with which we are all so familiar that we appear to know more about it than we really do."

Alterations in size and configuration of the clubbed digit result from changes in the nail bed, beginning with increased interstitial edema early in the process. As clubbing progresses, the volume of the terminal portion of the digit may increase because of an increase in the vascular connective tissue and change in quality of the vascular connective tissue, although some cases have been associated with spurs of bone on the terminal phalanx.

Although clubbing is a common physical finding in many underlying pathological processes, surprisingly, the mechanism of clubbing remains unclear. Different pathological processes may follow different pathways to a common end. Many studies have shown increased blood flow in the clubbed portion of the finger. Most researchers agree that this results from an increase in distal digital vasodilation, the cause of which is unknown. Also unknown is the exact mechanism by which increased blood flow results in changes in the vascular connective tissue under the nail bed. Many researchers agree that the common factor in most types of clubbing is distal digital vasodilation, which results in increased blood flow to the distal portion of the digits. Whether the vasodilation results from a circulating or local vasodilator, neural mechanism, response to hypoxemia, genetic predisposition, or a combination of these or other mediators is not agreed on currently.

Evidence that favors the presence of a circulating vasodilator derives from the association of clubbing with cyanotic congenital heart disease. Many potential vasodilators, which usually are inactivated as blood passes through the lungs, bypass the inactivation process in patients with right-to-left shunts. Patients with tetralogy of Fallot with substantial shunting have a high incidence of clubbing. After surgical correction diminishes the shunt, the clubbing improves. Also previously observed is clubbing confined to the feet in patients with late untreated patent

ductus arteriosus in whom blood from the pulmonary artery bypasses the lungs and is shunted into the descending aorta. In the absence of a shunt, the circulating vasodilator may be produced by the lung tissue, or, possibly, it passes through the pulmonary circulation without becoming inactivated. Proposed vasodilatory factors include ferritin, prostaglandins, bradykinin, adenine nucleotides, and 5-hydroxytryptamine.

A neural mechanism has been proposed with particular consideration of the vagal system. An increased incidence of digital clubbing has been associated with the pathology and disease of vagally innervated organs. Furthermore, regression of clubbing after vagotomy has been reported. Although some factor related to the vagal system is a possible contributor to the development of clubbing, especially clubbing occurring with hypertrophic osteoarthropathy, the hypothesis of a neural mechanism has decreased in popularity because of the lack of evidence of clubbing in neurologic disorders and the presence of clubbing in diseases of organs not innervated by the vagal system.

Hypoxia has been proposed as an alternative explanation for clubbing in cyanotic heart disease and pulmonary diseases. An increase in hypoxia may activate local vasodilators, consequently increasing blood flow to the distal portion of the digits; however, in most cases, hypoxia is absent in the presence of clubbing, and many diseases with noted hypoxia are not associated with clubbing.

Genetic inheritance and predisposition also may play a role in digital clubbing. Hereditary clubbing is observed in 2 forms, including idiopathic hereditary clubbing and clubbing associated with pachydermoperiostosis. The 2 forms are believed to be separate entities. Both demonstrate autosomal dominant inheritance with incomplete penetrance.

More recently, platelet-derived growth factor released from fragments of platelet clumps or megakaryocytes has been proposed as the mechanism by which digital clubbing occurs.[4] The fragments are large enough to lodge in the vascular beds of the fingertips, and, subsequently, they release platelet-derived growth factor. This factor has been shown to have general growth-promoting activity and causes increased capillary permeability and connective tissue hypertrophy.

The development of clubbing usually is gradual enough that many patients are unaware of its presence; however, some patients may report swelling of the distal portion of the digits, which may be bilateral or unilateral or may involve a single digit.

Although clubbing typically is painless, it rarely may present with pain in the fingertips.

Rapid postoperative resolution of clubbing in a few days was described in a patient with aortic and mitral valve replacement due to infective endocarditis.[6]

Hypertrophic osteoarthropathy may occur as an isolated calcaneal periostitis bilaterally.

Clubbing is a clinical finding characterized by bulbous fusiform enlargement of the distal portion of a digit

When the profile of the distal digit is viewed, the angle made by the proximal nail fold and nail plate (Lovibond angle) typically is less than or equal to 160°. In clubbing, the angle flattens out and increases as the severity of the clubbing increases. If the angle is greater than 180°, definitive clubbing exists. An angle between 160-180° falls in a gray area and may indicate early stages of clubbing or a pseudoclubbing phenomenon.

Individuals without clubbing display a diamond-shaped window at the base of the nail beds when the dorsum of 2 fingers from the opposite hands are opposed. The distal angle between the 2 opposed nails should be minimal. In individuals with digital clubbing, the diamond window is obliterated and the distal angle between the nails increases with increasing severity of

clubbing.

The nail moves more freely in patients with clubbing; therefore, the examiner may note a spongy sensation as the nail is pressed toward the nail plate. The sponginess results from increased fibrovascular tissue between the nail and the phalanx. The skin at the base of the nail may be smooth and shiny.

Causes

Clubbing can be idiopathic or secondary to many underlying pathologies in various organ systems.

Causes of idiopathic or primary clubbing include pachydermoperiostosis, familial clubbing, and hypertrophic osteoarthropathy.[8,9]

Causes of secondary clubbing include the following[10] :

- Pulmonary disease - Lung cancer,[11] cystic fibrosis, interstitial lung disease,[12] idiopathic pulmonary fibrosis,
[13]
sarcoidosis,
[14]
lipoid pneumonia, empyema, pleural mesothelioma, pulmonary artery sarcoma,
[15]
cryptogenic fibrosing alveolitis, lung hydatid cysts,
[16]
and pulmonary metastases (see Dermatologic Manifestations of Pulmonary Disease)

- Cardiac disease - Cyanotic congenital heart disease,[17] other causes of right-to-left shunting, and bacterial endocarditis (see Dermatologic Manifestations of Cardiac Disease)

- Gastrointestinal disease - Ulcerative colitis, Crohn disease, primary biliary cirrhosis, cirrhosis of the liver, leiomyoma of the esophagus, achalasia, and peptic ulceration of the esophagus (see Dermatologic Manifestations of Gastrointestinal Disease) [18]
- Skin disease - Pachydermoperiostosis, Bureau-Barrière-Thomas syndrome, Fischer syndrome, palmoplantar keratoderma, [19] and Volavsek syndrome
- Malignancies - Thyroid cancer, thymus cancer, Hodgkin disease,[20] and disseminated chronic myeloid leukemia (POEMS [polyneuropathy, organomegaly, endocrinopathy,

monoclonal gammopathy, and skin changes] syndrome is a rare paraneoplastic syndrome secondary to a plasma cell dyscrasia in which clubbing may be seen.
[21]

Other findings including peripheral neuropathy, organomegaly, endocrinopathy, monoclonal plasma proliferative disorder, skin changes, sclerotic bone lesions, Castleman disease, thrombocytosis, papilledema, peripheral edema, pleural effusions, ascites, and white nails.)

- Miscellaneous conditions - Acromegaly, thyroid acropachy, pregnancy, an unusual complication of severe secondary hyperparathyroidism, [22] and hypoxemia possibly related to long-term smoking of cannabis
[23]

Although as a paraneoplastic syndrome most commonly associated with non–small-cell lung cancer, it may occur with metastatic melanoma.[24]

Nail changes in 100 chronic renal failure patients undergoing hemodialysis and 100 matched controls were assessed.[25] Nail disorders were more prevalent in the renal failure patients (76%) than in the control group (30%). The half-and-half nail was the most common finding (20%), followed by absent lunula, onycholysis, brittle nail, Beau lines, clubbing, longitudinal ridging, onychomycosis, subungual hyperkeratosis, koilonychias, total leukonychia, splinter hemorrhage, pitting, and pincer nail deformity

Laboratory Studies

Because clubbing typically is secondary to an underlying pathological process, perform pertinent laboratory studies for primary medical disorders that are suggested clinically.

Imaging Studies

Radiographic changes in patients with digital clubbing vary and include bone dissolution, bone formation, or no change in the bone of the distal phalanx. The types of changes may depend on the underlying pathological processes, as well as the duration of the processes. The severity of soft tissue changes in clubbed digits has not been found to correlate with the type of bone change or the degree of radiographic change. Probably, the lysis of bone predominates in the

digits of patients with congenital cyanotic heart disease, while hypertrophy predominates in the digits of patients with clubbing secondary to pulmonary conditions. As an alternate view, hypertrophy may occur earlier in the process of clubbing, and, eventually, it may change to osteolysis as the process becomes chronic.

Technetium Tc 99m skeletal imaging with good-quality views may be helpful in determining the presence and extent of bone changes in clubbed digits, which show increased uptake of the radionuclide. The increased, intense, symmetric uptake typically is localized to the nail beds and may result from increased blood flow and changes in the surrounding soft tissues.

Thermography is another imaging modality being studied for use in diagnosis and monitoring of patients with digital clubbing.[26] Patients may show increased temperature in the distal digits, which can be attributed to an increase in blood flow secondary to vasodilation. Not all patients with clubbing have positive thermographic results.

Positron emission tomography also has been used to study the glucose metabolism of clubbed digits.[27] An increased signal, indicating increased glucose metabolism, has been demonstrated in the distal part of the clubbed fingers. These changes are not seen in fingertips with normal morphology. The increase in signal supports the theory that clubbing is caused by the presence of a factor (eg, platelet-derived growth factor) that increases cellular metabolism.

Other imaging studies, such as computed tomography or magnetic resonance imaging, may be helpful in evaluating the patient for the primary pathological process causing the clubbing.

Histologic Findings

Microscopically, the collagen fibrils and cells are separated by a distance greater than that seen in histologically normal specimens. This increased separation results in a less dense nail bed matrix. Primitive fibroblasts are seen with large nuclei, basophilic cytoplasm, and long reticular processes. Increased and scattered extravascular lymphocytes and, less often, a moderately increased number of tissue eosinophils also are noted in the nail beds of some specimens. The periosteum of the nail bed may be thickened with increased vascular penetration.

Eventually, increased collagen is laid down in all types of chronic clubbing. The mat of collagen fibers may be abnormally thick and dense. The walls of the vascular components increase in thickness and are encased in a thick fibrous sheet. At this stage of clubbing, the histologic and morphologic changes probably are irreversible

Medical Care

No specific treatment for clubbing is available. Treatment of the underlying pathological condition may decrease the clubbing or, potentially, reverse it if performed early enough. Once substantial chronic tissue changes, including increased collagen deposition, have occurred, reversal is unlikely. Treatment for related problems, such as pain, is symptomatic.

Surgical Care

No specific surgical procedures are performed for clubbing. Appropriate surgical treatment of underlying disease, such as tumor removal in patients with lung cancer, may improve or reverse clubbing, provided that permanent morphologic changes have not occurred.

Consultations

Clubbing is a clinical sign of many pathological processes; therefore, consultation with specialists may be necessary to diagnose the underlying disease. Patients with primary hypertrophic osteoarthropathy should be evaluated for associated findings, possibly including myelofibrosis.[28,29]

Medication

Definitive medical therapy is tailored to the underlying disease process and may include symptomatic treatment of the sequelae of clubbing.