treatment. Ninety percent of waiver requests for hypothyroidism were approved. Of those who were rejected, nearly all were rejected for other conditions not related to thyroid disease. For patients with subclinical hypothyroidism, a waiver is still required, but the patient does not require any treatment.[1] The U.S. Navy and U.S. Army similarly are willing to waive the diagnosis of hypothyroidism with documentation of a sufficient treatment and stable dose of levothyroxine.[11,14] The Navy also requires a waiver for subclinical hypothyroidism (TSH = 4.5-10 mIU/L) after 4-6 symptom-free weeks.[11] The Federal Aviation Administration includes hypothyroidism as a condition for which Aviation Medical Examiners can reissue an airman medical certificate under the provisions of an Authorization for Special Issuance of a Medical Certificate. Assuming the airman meets all requirements, the Aviation Medical Examiner can issue the certificate during the exam. All other cases must be referred back to the Aerospace Medical Certification Division or Regional Flight Surgeon.[3]

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You are a flight surgeon at an Air Mobility Command base. As you step off the C-17 one night at 22:00 after a 4-h training sortie following a full clinic day, you notice a senior loadmaster limping. Despite your fatigue and an 07:00 clinic tomorrow morning, you take a moment to trudge over and chat, then ask the loadmaster to come see you in clinic the next day. After the appropriate crew rest, this 40-yr-old male loadmaster is in your office describing atraumatic leg pain of 3 mo duration. It came on rather gradually and is not really limiting his activity. He has used no over-the-counter medications. He also admits a 20+ yr history of smoking a pack and a half per day, but otherwise has an unremarkable past medical history and social history. A review of systems reveals that he has no fatigue, fever, or weight loss. He has no abdominal pain or bowel complaints.

On examination you note normal head, ears, eyes, nose, throat, heart, lung, and abdominal exams, a slightly antalgic gait, bilateral

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bony tenderness of the long bones above and below the knee joints, and bilateral knee effusions. You also note generalized bilateral clubbing of the fingers and toes. You recognize this as true clubbing instead of pseudoclubbing because it is symmetric and there is a high profile angle of over 180°. The profile angle is the angle between the nail and the proximal nail fold, which is usually under 180°.[15] Additionally, pseudoclubbing is ordinarily associated only with one digit.[16] You find no evidence of lymphadenopathy.

1. Is the clubbing a concern?

A. Yes, it is associated with several pathological conditions.
B. Yes, its presence is prognostic whenever identified.
C. Yes, it is pathognomonic for one specific condition.
D. No, it is ordinarily an incidental finding.

ANSWER/DISCUSSION

1. A. Digital clubbing, which can be acquired or congenital, is localized growth of the distal portion of the digits caused by a proliferation of connective tissue between the nail matrix and the phalanx. This leads to enlargement all around the distal segment of the digit. Some have called it the oldest sign in clinical medicine, having been described first by Hippocrates nearly 2500 yr ago.[15]

Clubbing has also been associated with multiple disease processes. The primary diseases of concern include lung cancer, interstitial pulmonary fibrosis, lung abscess, pulmonary tuberculosis, bronchiectasis, and pulmonary lymphoma, while cardiovascular diseases such as congestive heart failure, infective endocarditis, and cyanotic congenital heart disease are possible. Clubbing is necessary to make the diagnosis of hypertrophic osteoarthropathy (HOA). It has also been found in gastrointestinal, infectious, endocrine, and psychiatric conditions, and others, but it can be an isolated finding.[3,15,16] Its prognosis depends on the underlying cause. Unilateral clubbing actually has somewhat of a distinct differential diagnosis and tends to involve neurological or vascular lesions.[16]

2. Which of the following is highest in your differential diagnosis?

A. HOA.
B. Inflammatory bowel disease.
C. Rheumatoid arthritis (RA).
D. Gout.

ANSWER/DISCUSSION

2. A. HOA is usually a secondary condition, characterized by clubbing, periostitis of long tubular bones, and symmetric arthritis.[4,8] Its most frequent cause is underlying lung cancer[8] and clubbing is frequently associated with lung cancer as well.[16] Inflammatory bowel disease is another recognized cause of digital clubbing[3] and arthritis is the most common extraintestinal manifestation.[1,20,21] However, only 38–58% of patients with Crohn's disease and about 15% of patients with ulcerative colitis have been reported to have clubbing. It is hardly considered sine qua non.[9] Clubbing is not associated with RA or gout.

Given our patient's history and physical, you believe that he is possibly suffering from secondary HOA. Clubbed fingers, painful symmetric polyarthritis, and periostitis of the long tubular bones make up the triad of clinical signs and symptoms.[4,8,10] You doubt primary HOA because it is a rare genetic disorder (also known as both pachydermoperiostosis and Touraine-Solente-Gole syndrome) that tends to present in adolescence with gradual thickening of the facial skin, neither of which seem to apply to him.[4,14,15] Since you have him in the office, you elect to aspirate the knees and find a serous effusion. The aspirate is sent to the lab.

In your research on secondary HOA, you have reminded yourself that the most frequent cause is found in the lungs and that the most common pulmonary cause is a neoplasm.[15] Indeed, it is estimated that 90% of adults with secondary HOA either have or go on to develop a malignancy.[16] When associated with a malignancy, HOA is considered a paraneoplastic syndrome.[17] Paraneoplastic syndromes are collections of symptoms associated with malignant diseases that are not directly related to the physical effects of the primary or metastatic tumors. The most frequent cell types of lung cancer associated with HOA are squamous cell carcinoma and adenocarcinoma, while the least commonly associated is small cell carcinoma. Because you are an unusually curious flight surgeon, you do further reading, which indicates the mechanism of clubbing and HOA in these patients remains uncertain, although one of the leading theories is that it could be related to the overexpression of vascular endothelial growth factor (VEGF).[17] According to this theory, megakaryocytes are ordinarily released from bone marrow and become entangled in pulmonary capillary beds, where they fragment into platelets. But in HOA, it is believed they bypass the pulmonary capillaries and enter the systemic circulation, where they lodge in the capillary networks of the digits. Here, they interact with the endothelial cells to release growth factors, including platelet-derived growth factor, prostaglandin E, and VEGF.[8]

3. Which of these diagnostic tests would you most like to obtain at this time?

A. Ultrasound.
B. Magnetic resonance imaging of the knees.
C. Pulmonary function test/spirometry.
D. Chest computed tomography (CT).

ANSWER/DISCUSSION

3. D. Identifying the underlying pathology is absolutely essential. A screening chest X-ray is an appropriate start in the evaluation of isolated clubbing, given our patient's history of bone and joint symptoms, and aggressive workup for malignancy is essential.[16,17] It is also the recommended first imaging study for possible lung cancer, while a volumetric chest CT is appropriate for clinical and

pretherapeutic staging of lung cancers.[2] Bone scintigraphy is a sensitive way to detect involvement of HOA in periostitis and the symmetric appearance with HOA can also help differentiate it from bony metastases when a known malignancy is present. X-rays of the knees would show periostitis and a lack of joint erosions, joint space narrowing, or subchondral sclerosis, differentiating HOA from RA or osteoarthritis.[4] However, these studies do not identify the underlying problem and, similarly, a magnetic resonance imaging of the knee would be of little value in detecting the primary condition, which is your job at this point. Ultrasound might also be helpful in identifying edema and inflammation around the long bones, but would not be diagnostic. Finally, lung spirometry holds value once a pulmonary process is identified, but it would be for evaluation of severity of lung function compromise and management, not for diagnosis.[10]

You begin imaging with a chest X-ray that shows a peripheral nodule in the right upper lobe. While the CT scan is on order, you order an erythrocyte sedimentation rate (elevated), serum alkaline phosphatase (elevated from periosteal bone formation), and synovial fluid analysis (noninflammatory, low cell count of <500/μL with predominantly lymphocytes and monocytes).[4,8] Complete blood count, comprehensive metabolic panel, and liver function tests are indicated in the workup of potential lung cancer, but are not otherwise remarkable in this patient.[10] You obtain X-rays of the knees that show periostitis of the tibia and femur, yet lack joint erosions, joint space narrowing, or subchondral sclerosis. Given the character of the knee aspirate and plain films, your suspicion that this is HOA rather than RA or osteoarthritis is confirmed,[4,8] and your primary concern remains lung cancer.

You make appropriate referrals for his care. The diagnostic workup and treatment plan require a multidisciplinary approach, including pulmonology, medical and radiation oncology, pathology, radiology, and cardiothoracic surgery. His ensuing workup includes a contrast-enhanced chest CT, a CT-guided transthoracic needle aspiration, and a functional evaluation.[10] The CT report confirms the presence of a 4.0-cm right upper lobe mass. He does have ipsilateral hilar lymph node involvement. Pathology shows an adenocarcinoma. Bone scintigraphy shows characteristic symmetric, bilateral increased uptake in the long bones without evidence of metastatic disease.[4,8] His stage is IIA-T2aN1M0. Functional assessment, including measurement of preoperative pulmonary function, calculation of predicted postoperative (postresection) pulmonary function, and exercise testing, indicates he would tolerate definitive lung resection well.

4. What is definitive treatment for this patient's HOA?

A. Medication.
B. Surgery.
C. Joint aspiration and intraarticular steroid injection.
D. Palliative treatment; HOA has no cure.

ANSWER/DISCUSSION

4. B. The key to resolving HOA is to treat the underlying cause. Of course, in this case the gravity of the underlying cause is much greater than the symptoms of the HOA. Surgical resection is indicated for stage I or II nonsmall cell lung cancer.[8,10] A majority of clubbing-associated malignancy is nonsmall cell, although some authors have noted a higher incidence of small cell carcinomas.[15] As previously noted, many studies indicate that adenocarcinomas predominate.[7,8,13] Unfortunately, 80% of newly diagnosed lung cancers are inoperable, owing to the fact that pulmonary nodules can grow for so long before causing symptoms, and the presence of constitutional symptoms often indicates metastatic disease. One Italian study found that when symptoms such as cough are related to the primary tumor, the 5-yr survival rate was approximately 12%, but when the presenting symptoms were nonspecific, the 5-yr survival fell to 6%. With metastatic disease in that population, the 5-yr survival was zero. A long delay between symptom onset and definitive diagnosis is common. However, the extent of a paraneoplastic disorder like HOA is not indicative of the size of the primary tumor.[17] Support exists for the position that detection of the paraneoplastic syndrome symptoms before the primary lung cancer becomes clinically evident is an advantage in that the tumor may be discovered in a more treatable stage.[11] Others report that presenting complaints of a paraneoplastic syndrome favor a poor prognosis.[10] A retrospective evaluation of 115 HOA patients with primary lung cancers (among 6151 lung cancer patients) revealed that surgical resection is superior to medical management alone for the improvement of HOA symptoms and signs,[13] but the ability to treat with resection is of course dependent upon the tissue type and stage.

5. What has been shown in case reports to be highly effective in treatment of refractory HOA?

A. Nonsteroidal anti-inflammatory drugs.
B. As-needed narcotic pain medication.
C. Bisphosphonates.
D. Physical therapy.

ANSWER/DISCUSSION

5. C. The best options on this list appear to be bisphosphonates, particularly pamidronate and zoledronic acid.[4,8,19] VEGF has been elevated in some patients with lung cancer and HOA,[17] and both bisphosphonates and the somatostatin analog octreotide are reported to inhibit VEGF.[8] Nonsteroidal anti-inflammatory drugs get mixed reviews.[4,8,19] Physical therapy is not mentioned in the literature as a viable treatment option for the symptoms of HOA. And while narcotics might be appropriate to manage the pain of cancers, they do not address the underlying cause of bony pain like bisphosphonates can.

His aeromedical disposition should be based upon the underlying pathology. Per the 2007 Lung Cancer Staging Project by the International Association for the Study of Lung Cancer, the mean survival time for clinical stage IIA is 34 mo, with 5-yr survival of 36%, while pathological stage IIA has a mean survival time of 49 mo and 46% survival rate at 5 yr.[6]

According to the Air Force Medical Standards Directory, secondary HOA is disqualifying for service only if associated with

severe pain in one or multiple joints and with moderate loss of function.* It is not mentioned specifically in the Air Force Waiver Guide, the U.S. Army Aeromedical Policy Letters and Aeromedical Technical Bulletins, or the U.S. Navy Aeromedical Reference and Waiver Guide.

Both military and Federal Aviation Administration (FAA) dispositions reflect the poor prognosis for lung cancers. The Air Force Waiver Guide has removed guidance for lung cancers, as well as several other malignancies, because of low numbers of cases available for evaluation and/or the poor prognosis and duration of treatment. A member being considered for a waiver would first undergo successful treatment and then be found suitable for retention under Medical Evaluation Board processing. He or she would then have a waiver package submitted that would include the following: history of tumor diagnosis, treatments, any side effects from the tumor or treatment; imaging reports, surgical, consult, and pathology reports, and clinically relevant labs; oncology consultation stating the malignancy is considered either cured or in remission and the recommended follow-up schedule for the patient; tumor board results if accomplished; and Medical Evaluation Board results.[18]

According to the U.S. Army Aeromedical Policy Letters and Aeromedical Technical Bulletins, the major aeromedical concerns for aviators with lung cancer are the risks of cerebral metastasis or pathological fractures and the possibility of diminished pulmonary function. Small cell lung cancers are not waiverable. Only primary nonsmall cell lung cancers of less than 2 cm may be considered. Positive lymph nodes will not be considered. To be considered for waiver, the aviator must be more than 3 yr out from initial diagnosis, fully recovered from therapy, and disease free.† The U.S. Navy Aeromedical Reference and Waiver Guide echoes the risk of cerebral metastasis and diminished pulmonary function. Waiver may be considered after successful resection of early stage carcinoma after 5 yr without recurrence.[12] The FAA Guide for Aviation Medical Examiners states that all malignant tumors or cysts of the lungs, pleura, or mediastinum are disqualifying for medical certification and require FAA decision.[5]

Our loadmaster undergoes successful resection without complication along with adjuvant chemotherapy, and his HOA symptoms resolve when using the bisphosphonate pamidronate for only a short time. This very fortunate member has no side effects following his treatment. He has biannual surveillance CT scans of the chest without evidence of recurrence for the first 2 yr. During this time he is processed through the Integrated Disability Evaluation System and, given his over 20 yr of active service, decides to retire. He also stops smoking.

* U.S. Air Force. Section K: spine and extremity USAF medical standards, K84. In: Medical standards directory. 2016:39. [Accessed 12 Nov. 2016]. Available from https://kx2.afms.mil/kj/kx4/FlightMedicine/Documents/Medical%20Standards%20Directory%20(MSD)/MSD%2011%20September%202016%20(final%20draft).pdf to those with access.

† U.S. Army Aeromedical Activity. Lung cancer. In: Aeromedical policy letters and aeromedical technical bulletins. Ft. Rucker (AL): U.S. Army Aeromedical Activity; 2015:145. [Accessed 9 Oct. 2016]. Available from https://vfso.rucker.amedd.army.mil/public/downloads/Army_APLs_May2015.pdf to those with access.

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