

Letters to the Editor

Erratum

In the May 1997 issue of the *Annals of Saudi Medicine* (Volume 17, Number 3), the name of J. Fernando Val-Bernal, MD, was mistakenly omitted from the letter to the editor entitled "Myoepithelioma of the submandibular gland occurring after cardiac transplantation." Dr. Val-Bernal was in fact the senior author of this letter. He is Professor and Chairman of Anatomical Pathology at the University of Cantabria Medical School in Santander, Spain. We apologize for this omission.

Adverse Reaction to Heparin Products: A Case Report

To the Editor: In high-risk procedures, some form of heparin should be used as prophylaxis (NHCC 1986; ECC 1992; THRIFT 1992). The standard management and prophylaxis of deep vein thrombosis is anticoagulation initially by heparin. We have had an unusual experience with heparin and its products. It is so uncommon to have a hypersensitive reaction to heparin that one should be aware of this possibility to avoid a fatality. It is well established that heparin can produce thrombocytosis in certain patients, rather than thrombocytopenia.

A 67-year-old female was admitted for open reduction internal fixation of fractured femur. She was commenced on unfractionated heparin 5000 units subcutaneously three times a day, as prophylaxis against deep vein thrombosis. Immediately following injection she complained of severe pain at the injection site and inability to move the arm.

On examination, it was noted that there was swelling and bruising of the affected arm and blister formation at the injection site. Suspecting intolerance to heparin, the injections were discontinued. However, postoperatively, she complained of pain in the left calf and leg, which also became swollen. Suspecting deep vein thrombosis, she was commenced on low molecular weight heparin (enoxaprin) 40 mg subcutaneously. She immediately developed a severe local reaction with pain, erythema and blister formation at the injection site. The enoxaprin was discontinued pending results of venogram. However, in the face of confirmed deep vein thrombosis in the venogram, it was imperative to commence some anticoagulation therapy for this patient. The patient was started on intravenous infusion of unfractionated heparin bolus dose of 5000 unit subcutaneously, to be followed by continuous infusion. Within minutes of the bolus injection, the patient complained of crampy abdominal pain and shortness of breath, and also became bradycardic. Heparin was discontinued immediately and the patient was treated for anaphylactic shock, with prompt response. Ventilation

perfusion scan failed to show any evidence of pulmonary embolism. Blood investigations revealed that platelet count was 328,000 U/L and rose to 468,000 U/L. Her deep vein thrombosis was treated with warfarin. She made a good recovery and was eventually discharged home. We conclude that her hypotensive bradycardic episode was a result of hypersensitivity to heparin because of severe localized reaction following intravenous injection.

Most cases reported of heparin-induced anaphylaxis on record include patients with thrombocytopenia, possibly secondary to platelet consumption following enhancement thromboxane A₂ synthesis induction of normal platelet aggregation, and in some cases, due to the presence of heparin-induced platelet-aggregating factor. In our patient, the opposite phenomena was observed, with a rise in platelet count. This, however, does not exclude consumption, since increase in platelet production may overshadow mild to moderate platelet consumption. The increase in platelet number may lead to increase in platelet aggregation, which may be the possible etiology of pulmonary embolism.

Idiosyncratic reactions occur in 5% of cases of heparin therapy, therefore, the risk from hemorrhage increases in these patients, and life-threatening complications can occur. Mortality of up to 30% has been noted. Patients can develop stroke, myocardial infarction and spinal artery thrombotic episodes if not recognized.

Heparin-induced thrombocytopenia (HIT) may lead to peripheral occlusion, myocardial infarction, gangrene, hemiplegia and death. HIT varies from 0% to 30%, but despite severe thrombocytopenia, bleeding is rare.

HIT-induced thrombosis occurs with the onset of thrombocytopenia and continues even with the withdrawal of heparin. Arterial thrombosis may lead to gangrene of lower limbs, stroke, acute myocardial infarction, end organ failure such as renal failure, and deep vein thrombosis.

Disseminated intravascular coagulation defect may lead to multiple hepatic infarctions, hemorrhagic adrenal necrosis and skin necrosis. HIT patients may have mortality of up to 30%, and approximately 20% have a risk of leg amputation.

The reaction in our patient following heparin administration may be due to type 1 sensitivity reaction, as she had no previous documented exposure to heparin products, or it may have been due to platelet release of vasoactive substances. It is, therefore, clear that anaphylactic reactions following heparin administration do occur, and that they may be severe and possibly fatal. It is our opinion that awareness of this possibility would allow early recognition and prompt treatment, and hopefully avert a fatality.

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The Arteries in Tuberculosis

To the Editor: I read with great interest the paper by Husen et al.,¹ describing the multimodality radiological imaging of hepatic artery aneurysm, and attributing its etiology to the presence of caseous granulomata in the nearby abdominal lymph nodes which were "consistent with tuberculosis." The case was erroneously reported as "tuberculous hepatic artery aneurysm." I would like to offer an overview of reaction of arteries to tuberculous infection and criticize the approach of the above paper towards the association of tuberculosis, arteritis, and aneurysm.

While we agree that hepatic artery aneurysms are rare, tuberculous of this site is probably never reported. The estimated incidence of primary hepatic artery aneurysm is less than 0.25%,² and about three or four cases, mostly saccular, are reported annually. Primary dissecting aneurysms unaccompanied by aortic dissection are even rarer, and only about 14 have so far been reported.^{3,4} Arteries involved in tuberculous inflammation usually show features of progressive endarteritis obliterans, leading to complete obliteration of the small vessels, and as caseation spreads their structural organization is lost. This is a reactive process of the small arteries against many long-standing chronic inflammatory processes. On the other hand, the adventitia and the medial coats of the arteries may gradually be eroded from adjacent caseous tuberculous cavity of lymph nodes, thus weakening the vessels and

leading to the formation of Rasmussen's aneurysm. But in this case, it is a compilation of a nearby tuberculous lesion rather than primary involvement of the vessel. The term "tuberculous arteritis" must be reserved for cases of caseous granulomata with either positive AFB or bacterial culture involving the media and adventitia of major vessels, following miliary dissemination of bacilli through the vasa vasora.

In the above paper, the fact that the "lymph nodes adjacent to the aneurysm showed caseating granulomas consistent with tuberculosis" does not mean that the artery is affected unless there is histological evidence, nor does it mean that the lesion is actually tuberculous because of the absence of confirmatory (i.e., laboratory) evidence of tuberculosis. None of these criteria are mentioned in the paper. On the other hand, the term "consistent" is widely used by pathologists to give a diagnosis based on the interpretation of the clinical, radiological and morphologic microscopic appearances which can occur in a number of other pathological lesions and in which the confirmatory (i.e., laboratory) evidence (such as conventional special stains, immunohistochemical markers, electron microscopy, etc.) either reveal a negative result or have not been done. In the case of tuberculosis, pathologists use the term "consistent" when the conventional stains used in the histology laboratory fail to demonstrate the tubercle bacilli. In the above case, there is no mention of whether the hepatic artery aneurysm was of the saccular or dissecting type, and whether the histological examination of arterial wall contained any caseous granulomata. In addition, there is also no mention of whether acid-fast bacilli were seen in abdominal lymph or the hepatic artery, and if not, whether bacterial culture was successful in growing and demonstrating these bacilli. Without these routine criteria, the case remains consistent with abdominal tuberculous lymphadenitis only and not arterial tuberculosis.

Finally, the description of the above case report is incomplete, since it does not satisfy the curiosity of interested readers who would want to know what happened to the patient after the ligation of the hepatic artery. This is important not only to complete the case description, but also to prepare readers should they become involved in a similar case. It would seem here that the editors of the *Annals* may share responsibility in permitting an unqualified work into the scientific literature.

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Reply

To the Editor: We would like to thank Dr. Al-Hilli for his corrective feedback on the above-mentioned article and give the following explanation.

Specimen slides were reviewed by a pathologist. Many granuloma were seen with caseation necrosis in lymph nodes adherent to the vessel wall. As Dr. Al-Hilli has mentioned, an aneurysm in this location might have resulted from weakening of the vessel wall due to caseation in an adjacent lymph node. We accept the above-mentioned mechanism for the development of the aneurysm. However, it is still an unusual occurrence for aneurysmal development in relation to abdominal tuberculous lymphadenitis. We thank Dr. Al-Hilli once again for taking an interest in the article and critiquing it in a positive way.

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Ectopic Thymus Presenting as a Neck Swelling in a Newborn

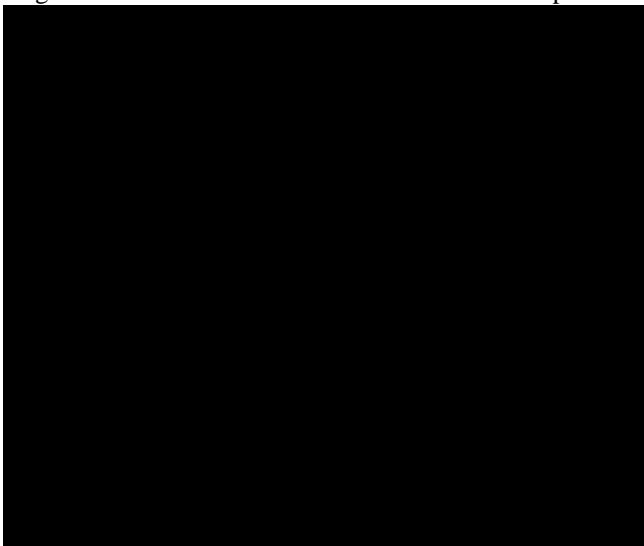
To the Editor: The differential diagnosis of a neck swelling in a child commonly includes cervical lymphadenopathy, branchial cyst, thyroglossal cyst and cystic hygroma. The thymus gland is usually located in the superior mediastinum, but because of its embryological origin it can be found ectopically in any location along a line extending from the embryological position in the neck to the final position in the superior mediastinum.¹ Although ectopic cervical tissue is not an uncommon finding during autopsy studies,^{2,3} very few enlarge to present clinically. Ectopic cervical thymus should be considered in the differential diagnosis of cervical masses in children. This is a report of

FIGURE 1. CT scan of the neck showing a mass on the right side of the neck.

an ectopic cervical thymus presenting as a cervical mass in a newborn.

A three-month-old baby, a product of full-term normal vaginal delivery to a gravida 2 para 2 mother, was admitted to our hospital because of a right-sided neck swelling. The mother noticed the swelling immediately after birth, and reported it to be increasing in size. Physical examination revealed a healthy-looking baby with no other abnormalities apart from a soft spongy irregular swelling on the right side of the neck. The swelling measured 3 x 4 cm in size and extended from just behind the ear above to the angle of the mandible below. The blood CBC, chemistry and chest x-ray were normal. Ultrasound and CT scan of the neck revealed a mass which was deep to the lower part of the parotid gland and under the sternocleidomastoid muscle laterally and the carotid sheath posteromedially. The mass measured 3 cm sagittally and 2.5 cm anteroposteriorly and was most likely lymphatic in origin (Figure 1). A normally placed thymus was seen on CT scan. Fine-needle aspiration biopsy was performed but the report was inconclusive. The patient was operated on and the mass was excised totally, together with an adjacent enlarged lymph node. Histology of the lymph node revealed reactive lymphadenitis, while that of the mass showed it to be thymus. This was identified by the medullary region containing multiple Hassal's concentric corpuscles of epithelial cells. There was no evidence of malignancy and no thyroid tissue was seen. Postoperatively, the patient did well and was discharged home on the third postoperative day.

Embryologically, the thymus gland starts to develop at about the sixth week of intrauterine life as a paired primordia from a ventral sacculation of the third pharyngeal pouch. These elongate caudally as the tubular structures known as thymopharyngeal tracts. At about seven weeks of intrauterine life, the two tracts after separation and proliferation incompletely fuse in the midline, forming the thymus gland which (because of its attachment to the pericardium) descends into the superior mediastinum to lie anterior to the pericardium and great vessels.⁴ As a result of this, thymic tissue is sometimes seen along the descent line of the thymus from the original position in the neck to the



final position in the superior mediastinum.¹ Noback in an autopsy study of 65 random infants reported an 80% incidence of ectopic cervical thymus tissue,² but the incidence of clinically apparent ectopic thymic tissue is rare.³ This is because only a few of these enlarge to become visible or cause symptoms. Whereas ectopic thymic tissue can be found commonly along the line of descent of the thymopharyngeal tracts, it is less often found in other sites, including the base of the skull, pharynx, neck and posterior mediastinum.⁵ The presence of ectopic thymic tissue at these sites was explained by the loss and sequestration of a part of the developing thymus, leading to its migration with local tissues.⁵ Of all these sites, ectopic cervical thymus is reported to be the most common. It is usually apparent clinically, while asymptomatic ectopic thymic tissue at other sites is difficult to diagnose and may produce symptoms in the form of dysphagia or airway compression.^{3,6}

Although ectopic cervical thymus is the most common of all types of ectopic thymus, the diagnosis in all is not suspected preoperatively, and is confirmed only after excision and histological examination. Ultrasound and CT scan in our case were not helpful. Fine-needle aspiration was tried in our patient but the result was inconclusive. Intraoperatively, these masses classically lie along the carotid sheath deep to the sternocleidomastoid muscle.

Ectopic cervical thymus, although rare, should be borne in mind when considering the differential diagnosis of cervical masses in infants and children. To obviate the risk of possible malignant transformation which has been reported in aberrant cervical thymus and to confirm the diagnosis, excision of these lesions is mandatory.

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Doxycycline-Induced Esophageal Ulceration

To the Editor: The entity of pill esophagitis was first described in 1970, and since then more than 200 cases of drug-induced esophageal ulcerations have been reported.¹ In spite of repeated emphasis, the list of drugs incriminated in the causation of esophageal ulceration keeps increasing. The most common injurious drugs are doxycycline hydrochloride and emepronium bromide, but more than 20 different drugs have been reported to induce esophageal ulcerations.^{2,3} Awareness of this potential complication among physicians is of great importance, as it is preventable and most of the time easy to treat. This report describes two cases of doxycycline-induced esophageal ulceration, highlighting points pertinent to diagnosis, treatment and prevention.

Case 1

A 35-year-old male presented with odynophagia and hematemesis of 10 days' duration. Two weeks prior to presentation, he had taken doxycycline for an upper respiratory tract infection. There was no history of previous

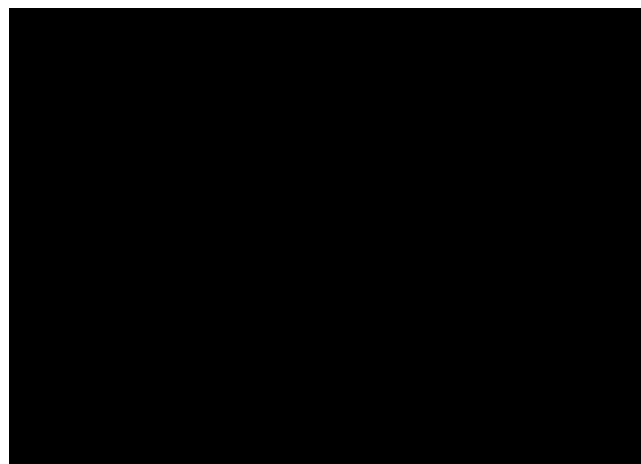


FIGURE 1. Two kissing ulcers in the upper third of the esophagus. similar attacks, peptic ulcer disease or liver disease, and no previous history of caustic ingestion. Clinical examination was normal as well as barium swallow. Upper gastrointestinal endoscopy revealed an ulcer in the middle third of the esophagus. Histology of the ulcer revealed nonspecific inflammation. The patient was advised to discontinue the use of doxycycline and to take viscous xylocaine and antacids as needed. Repeat endoscopy after two weeks showed complete healing of the ulcer.

Case 2

A 34-year-old male presented with odynophagia and chest pain of three days' duration. Five days before presentation, he had taken doxycycline for an upper respiratory tract infection. Clinical examination was normal. Upper gastrointestinal endoscopy revealed two

kissing ulcers in the upper third of the esophagus (Figure 1). The patient was advised to discontinue the use of doxycycline and to take antacids and sucralfate as needed. Repeat endoscopy after two weeks revealed complete healing of the ulcer.

There is no doubt that several drugs induce esophageal ulceration as side effects, but the true frequency of drug-induced esophageal ulceration is probably underestimated for two reasons. The main reason is failure to identify, properly diagnose and report many cases in the literature. The second reason is due to the fact that these lesions are usually mild, self-limiting and so underdiagnosed.⁴ Although the symptoms are often self-limiting and most cases resolve within days to a week, sometimes the symptoms may be severe and long lasting, and on occasion can be fatal.^{2,4,5}

Drug-induced esophageal ulceration has been demonstrated in animals, but the exact pathogenesis remains unknown. There is some evidence that a transient weakness of esophageal peristalsis may be the primary factor which acts in conjunction with a locally induced specific drug toxicity, leading to caustic injury of the esophageal mucosa.² The caustic injury is less with the coated form of doxycycline, so if doxycycline is to be given, the coated form should be prescribed for all patients.¹ Patient education in this regard is of great importance, and it is the responsibility of the treating physician and pharmacist to inform them of such possibility and advise them to take adequate fluids (approximately 100 cc) when swallowing the capsule, and take while standing for about 30 minutes before lying down. Although patients with underlying esophageal abnormalities such as motility disorders, hiatal hernia, achalasia, Schatzki's ring, reflux-induced esophagitis and

stricture are more likely to have drug-induced esophageal ulceration, it is not uncommon for healthy individuals to be affected.^{2,5}

The diagnosis in these cases is usually made on the basis of a classic history of recent drug intake, in conjunction with the macroscopic appearance of the lesion during endoscopy. The patient typically takes a tablet late at night with little or no fluid and then goes to bed to awaken a few hours later or early in the morning with severe retrosternal pain and odynophagia, neither of which is relieved by drinking or eating. The majority of drug-induced esophageal ulcerations occur in the middle third at the level of the aortic arch, and less commonly in the upper and lower third. Endoscopy may reveal a circumscribed redness or friability of the mucosa, an erosion about the size of a coin, or an ulcer which can be superficial or deep. The lesions can be multiple, and kissing ulcers are often seen, as was the case in our second patient. Biopsy will show nonspecific inflammatory changes.

There is no specific therapy for drug-induced esophageal ulceration. The pain usually subsides within one week, however, it may take up to six weeks for the ulcer to heal. The patients are advised to stop taking the offending drug. For severe retrosternal pain, local anesthetics (viscous xylocaine) are used in addition to systemic analgesic therapy. The role of antacids and H₂ receptor-antagonists in these cases is not known, although they are commonly prescribed. Most lesions heal without sequelae, but esophageal stricture is a known late complication.²

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