Death due to primary hyperparathyroidism

Gulbin Aygencel, MD, Ayfer Keles, MD, Ahmet Demircan, MD.

Asymptomatic hypercalcemia is a common metabolic disorder, usually detected incidentally on routine biochemical screening. The most common etiologies are primary hyperparathyroidism (PHPT) and cancer. Primary hyperparathyroidism is characterized by excessive parathyroid hormone (PTH) secretion due to parathyroid adenoma (80% of cases), hyperplasia (15-20%), and carcinoma (1-2%). Primary hyperparathyroidism is usually mild and asymptomatic. Only a few patients with PHPT develop hypercalcemic crisis, a medical emergency characterized by severe hypercalcemia with serum calcium concentrations above 3.8 mmol/L and marked symptoms and signs of severe calcium intoxication. The symptoms are frequently nonspecific with gastrointestinal, renal, neuromuscular, cardiovascular, and central nervous system dysfunctions. Here, we report a case of extreme hypercalcemia (serum calcium level of 6 mmol/L) associated with parathyroid adenoma, the patient died due to a cardiovascular complication (arrhythmia) of hypercalcemia.

A 45-year-old woman was admitted to our emergency department with a 20-day history of nausea, anorexia, vomiting, and muscular weakness. She denied any previous illness. There was no family history of any illness. On admission, she appeared dehydrated and extremely tired, almost apathetic, but had no focal neurological signs. Biochemical assays revealed extreme hypercalcemia, 24 mg/dL (6 mmol/L, normal range 10-65), confirmed by repeated measurements. Serum creatinine and urea levels were mildly elevated, indicating a slight renal affection. Electrocardiography showed a sinus tachycardia with a normal axis and QT interval. She received intravenous normal saline, loop diuretics, bisphosphate, and calcitonin to decrease the calcium concentration. The initiated treatment was not successful to reduce the serum calcium level, and hemodialysis was performed. Her PTH level was found to be significantly elevated, 5670 pg/mL (normal range 10-65). Ultrasound examination revealed a parathyroid adenoma measuring 5 cm in diameter, with a cystic component. Surgical exploration was planned, but she died before operation due to a cardiovascular complication (arrhythmia).

Hyperparathyroid crisis, first documented in man in 1939, is a rare but often fatal condition. Although the mortality rate has been reduced lately, as a result of earlier diagnosis and better intensive care management, patients are still dying due to inappropriate symptomatic treatment before surgical intervention or delay in surgery. Our patient was admitted to the hospital with a short duration. She presented with all the typical symptoms and signs of a hypercalcemic syndrome. The highly elevated PTH concentration and the mass lesion that were found on the ultrasonography confirmed the diagnosis of PHPT. There is no clear correlation between serum calcium level, symptoms and mortality except at a very high calcium levels. In the literature, we found only few cases with high calcium levels (6.9-7.6 mmol/L) and resulted in death. In cases of benign parathyroid disease, it is often unclear what leads to the exacerbation of the condition. Sometimes, rapid growth with partial necrosis or infarction of the parathyroid adenoma may be the reason. Acute cystic degeneration of preexisting parathyroid adenoma can also result in marked acute elevations of serum PTH and calcium levels. We think that this also occurred in our case. As medical therapy alone rarely restores normocalcemia, surgical exploration of the neck and resection of the hyperfunctioning parathyroid tissue should be performed without further delay. We also planned to operate on the patient, but she died before operation.

In summary, despite all advances in this field, hypercalcemic crisis in hyperparathyroidism still carries a significant risk of mortality, especially in patients with extremely high serum calcium levels.

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From the Department of Emergency Medicine, Gazi University Faculty of Medicine, Ankara, Turkey. Address correspondence and reprint requests to: Dr. Gulbin Aygencel, Department of Emergency Medicine, Gazi University Faculty of Medicine, Besevler 06510, Ankara, Turkey. Tel. +90 (312) 2025041. Fax. +90 (312) 2230528. E-mail: gencel69@hotmail.com

References

Ventricular septal rupture presenting with hyperosmolar hyperglycemic nonketotic coma

Ersan Tatli, MD, Huseyin Surucu, MD, Mutlu Buyuklu, MD, Mustafa Yilmaztepe, MD.

Hyperosmolar hyperglycemic nonketotic coma (HHNC) is a life-threatening emergency manifested by marked elevation of blood glucose, hyperosmolarity, and little or no ketosis. With the dramatic increase in the prevalence of type 2 diabetes and the aging population, physicians may encounter this condition more frequently in the future. Although the precipitating causes are numerous, underlying infections are the most common. Other causes include certain medications, undiagnosed diabetes, substance abuse, acute myocardial infarction (AMI), and coexisting disease. Although the coexistence of AMI with other clinical manifestations of diabetes has been well described, few data exist on the concomitant occurrence of HHNC and myocardial infarctions. This article aims to discuss the clinical course and treatment strategies of this rare condition.

The mortality rate of HHNC is between 10-50%, a considerably higher rate than that of diabetic ketoacidosis. Age, degree of dehydration, hemodynamic instability, underlying precipitating causes, and degree of consciousness all are powerful predictors of a fatal outcome.1 Coronary artery disease is the leading cause of mortality in patients with diabetes mellitus, which accounts for a considerable amount of comorbid conditions of patients suffering an AMI.2 At hospital admission, these patients may demonstrate a large clinical spectrum of disease, varying from newly diagnosed diabetes to a diabetic coma. Diabetic ketoacidosis and HHNC are 2 types of life-threatening diabetic comas that are associated with or precipitated by an AMI in rare conditions. Although AMI has been reported to be a frequent cause of death in diabetic ketoacidosis, there is little on the association of HHNC with acute coronary syndromes. Herein, we describe the clinical courses and treatment approach of a patient with ventricular septal rupture after AMI.

A 60-year-old woman was admitted to our emergency department with the complaints of severe shortness of breath and angina radiated to the left arm and hand. No heart disease, hypertension, diabetes mellitus, or drug use was present in her history. She was orthopneic and cyanotic. Blood pressure was 90/60 mm Hg; heart rate was 106 bpm. Jugular venous distention, third heart sound, continue murmur through the left sternal line and inspiratory crepitant pulmonary rales were detected on her physical examination. An electrocardiogram (ECG) showed diagnostic ST segment elevations in DII, DIII, aVF and V5-V6. On echocardiography, ventricular septal rupture, and akinesia in the inferior, posterior and lateral walls of the left ventricle were seen. Blood glucose was 885 mg/dl, creatine kinase, myocardial bound was 99 U/L, and leukocyte count was 16000/mm³. She was transferred to the coronary care unit with the diagnosis of inferolateral AMI and HHNC. Serum osmolality was 350 mosm/kg. Urine analysis revealed glycosuria associated with only mild ketonuria. Arterial blood gas analysis showed mild acidosis. Thrombolysis was started with streptokinase. However, the patient developed cardiopulmonary arrest during the infusion and did not respond to cardiopulmonary resuscitation. Type 2 diabetes is an important cause of cardiovascular morbidity and mortality accounting for 20% of the total number of patients admitted for suspected myocardial infarction. Patients with diabetes have a 2-fold increase in hospital mortality when compared with those without diabetes. Long-term follow-up reveals a continuously increasing excess mortality, mostly due to fatal re-infarctions and congestive heart failure.2 Acute MI causes a dramatic increase in adrenergic tone, which stimulates lipolysis, thereby increasing the levels of free fatty acids. Several hormonal mechanisms contribute to a decrease in insulin sensitivity and glucose utilization during acute myocardial ischemia. Recently, published data have suggested that acute hyperglycemia and poor glycemic control independently contribute to the increased cardiovascular risk of diabetes mellitus.3 The DIGAMI study,4 which demonstrated a linear relationship between blood glucose tertiles and long-term mortality, suggested that strict insulin treatment with improved metabolic control seems to reduce the adverse effect of an initially poor metabolic control. Acute hyperglycemia impairs coronary microcirculatory response to myocardial ischemia, attenuates the endothel-dependent (stem from the endothel) vascular response, inhibits nitric oxide production, and increases free oxygen radicals.4 Both hyperglycemia and hyperosmolality that are characteristic features of HHNC might associate to an increased extent of an AMI. In diabetic and acutely hyperglycemic dogs, infarct size was found to be linearly related to blood glucose concentration.5 Although hyperosmolality has been reported to increase left ventricular contractility and oxygen consumption, it’s independent contribution to the infarct size is controversial, and even a decrease in infarct size by increasing serum osmolality has been observed.5 Our patient suffering both AMI with ventricular septal rupture and HHNC had a complicated clinical course at the acute phase. Interestingly, diabetes mellitus was not in her history.
In conclusion, underlying precipitating causes should be investigated in patients presenting with HHNC. Mortality seems high in patients presenting with HHNC and AMI. Perhaps, it is necessary to investigate new treatment approaches to reduce mortality in these patients.

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From the Department of Cardiology, School of Medicine, Trakya University, Edirne, Turkey. Address correspondence and reprint requests to: Dr. Ersan Tatlı, Department of Cardiology, School of Medicine, Trakya University, Edirne, Turkey. Tel. +90 (28) 42357641. Fax. +90 (28) 42357652. E-mail: ersantatli@hotmail.com

References


A forgotten complication following pancreatic resection. Visceral artery pseudo-aneurysms

Yao-Kuang Huang, MD, Ming-Shian Lu, MD, Feng-Chun Tsai, MD, Po-Jen Ko, MD, Hung-Chang Hsieh, MD, Pyng-Jing Lin, MD.

Postoperative bleeding after pancreaticoduodenectomy (PDR), with an incidence of 7.5%, is not an uncommon complication. Most of the bleeders comprised operative field and gastrointestinal ulcers at the anastomotic margin. Visceral artery aneurysms as a bleeding source following PDR, although rare, are clinically important, and potentially lethal without prompt recognition. Despite recent advances in therapeutic techniques and diagnostic tools, the management of visceral artery aneurysms following PDR remains clinically challenging. We analyzed the initial presentations, therapeutic interventions, and outcomes of 5 patients with complicating visceral artery aneurysms after PDR, followed by a review of pertinent clinical information. Data were collected retrospectively on all patients receiving PDR and diagnosed with visceral artery aneurysms that occurred between June 2000 and June 2005. Table 1 lists the demographics and clinical outcomes of these 5 patients. Four patients received one-stage PDR (Whipple's operation) for pancreatic head cancer. Duodenum-preserving pancreatic head resection was deployed in one patient with benign pancreatic lesion. Four out of 5 (80%) patients presented as gastrointestinal bleeding. One patient (20%) presented as bleeding from abdominal drains, and had no additional episode before visceral artery pseudo-aneurysms was proven. The interval from pancreatic resections to definitive diagnosis of visceral artery pseudo-aneurysms was 20.6±7.8 days (range, 10-30 days). Three common hepatic artery, and 2 gastroduodenal artery pseudo-aneurysms were proven in the diagnostic angiography. Common hepatic artery pseudo-aneurysms were treated by coil embolizations of the common hepatic artery (Figure 1). Pseudo-aneurysms in the gastroduodenal artery obliterated all feeding arteries as in case 4, or occluded the pseudo-aneurysm per se as in case 5. The only in-hospital death had received PDR for pancreatic cancer and was discharged on post-operative day 14th. The patient returned to the emergency department on post-operative day 20th owing to jaundice, severe upper gastrointestinal bleeding, and hypovolemic shock. Emergency arterial angiography disclosed a common hepatic pseudo-aneurysm, which ruptured into the gastrointestinal tract. Although hemostasis was temporarily achieved by transcatheter coil embolization, the patient eventually succumbed as a result of multi-organ failure. There were 2 deaths in the follow-up; one died of intra-abdominal abscess in the 3rd month, and the other died of liver abscess in the 22nd month. The mean follow-up (excluded one in-hospital mortality) was 21.25±16.58 months, range 3-43 months.

Brodynsky and Turnbull reported a “sentinel bleed” after PDR that was attributed to vessel erosion. Fresh bloody discharge from abdominal drains comprised most initial presentations of “sentinel bleed.” Relevant clinical research also had similar observations, with an average presentation of 19 days after PDR. In this
**Table 1** - Demographics and clinical outcomes.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/Age</th>
<th>Surgical Procedures</th>
<th>Pathology</th>
<th>Presentation</th>
<th>Interval (days)</th>
<th>Aneurysm site</th>
<th>Intervention for visceral artery aneurysms</th>
<th>In-hospital death</th>
<th>Follow-up</th>
<th>Final Status</th>
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<td>None</td>
<td>Recurrent bleeding</td>
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<td>UGIB</td>
<td>10</td>
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<td>Occlusion of common hepatic artery by 4 coils</td>
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<td>Died in 22nd month</td>
<td>Liver abscess</td>
</tr>
<tr>
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<td>20</td>
<td>Common hepatic artery</td>
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<td>Poorly differentiated adeno-carcinoma</td>
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<td>Gastroduodenal artery</td>
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<td>No</td>
<td>Alive in 17th month</td>
<td>Liver metastasis</td>
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<td>F/65</td>
<td>Duodenum-preserving pancreatic head resection Roux-en-Y pancreatic-jejunostomy</td>
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<td>UGIB</td>
<td>30</td>
<td>Gastroduodenal artery</td>
<td>A saccular pseudoaneurysm in the middle third of the gastroduodenal artery. Fulfil aneurysmal sac by 2 coils</td>
<td>No</td>
<td>Died in 3rd month</td>
<td>Intra-abdominal abscess</td>
</tr>
</tbody>
</table>

PDR - Pancreaticoduodenectomy; UGIB - Upper gastrointestinal bleeding; Interval (days): interval from pancreaticoduodenectomy to clinical presentation.

**Figure 1** - An example of endovascular treatment of visceral artery pseudoaneurysm after pancreatic resection in case 3; a) Angiographic survey for intermittent gastrointestinal bleeding after Whipple’s operation demonstrated an out-pouch from common hepatic artery, which was compatible with pseudoaneurysm. Black arrow indicates the pseudoaneurysm. b) Common hepatic artery was trapped with four pieces of metallic coils. The followed angiography revealed total occlusion of the pseudoaneurysm and common hepatic arterial flow. White arrow indicates the blind end of common hepatic artery.
study, the interval from PDR to definitive diagnosis of visceral artery aneurysms was 20.6±17.8 days (range, 10-30 days). However, only one patient in our series presented as fresh blood in the abdominal drains. Eighty percent (4/5) presented a diagnostic enigma, as the gastro-intestinal bleeding is the sole manifestation. Their definite diagnoses were obtained by angiography arranged following a negative pan-endoscopic examination for peptic ulcer.

Surgical exploration and identification of the bleeding vessels may be difficult and hazardous due to the surrounding of post-surgical tissue friability. Bowel adhesion and anatomic variation following PDR further complicated the treatment. Endovascular intervention thus became the preferred treatment option for aneurysms disclosed in the angiography for indeterminate gastrointestinal bleeding after PDR. Aneurysms of the hepatic artery were treated via total exclusion without vascular reconstruction. Collateral circulation is usually sufficient through the superior mesenteric artery to the gastroduodenal artery. In cases of pancreatoduodenal and gastroduodenal artery aneurysms, hemostasis is often difficult due to multiple communicating vessels. Endovascular coil embolization during angiographic study is advantageous over surgery in easily identifying and obliterating all the feeding arteries to the aneurysm in cases with such anatomic restrictions. Prompt endovascular coil embolization achieved 80% short-term success in this series. The only hospital death was caused by profound hypovolemic shock prior to resuscitation. Two late deaths directly were attributed to infection, which reflected the immuno-compromised status of the patients. In addition, one survivor was proven with liver metastasis at 17th month follow-up. Although the long-term outcomes of visceral artery aneurysms following PDR are less favorable, the endovascular approach still provides adequate efficiency within their limited life expectancy.

In conclusion, successful treatment of visceral artery aneurysms following PDR requires a high index of suspicion, early diagnosis, and timely treatment. The endovascular intervention is feasible in such conditions. Clinical practitioners associated with pancreatic disease should be familiar with this scenario.

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From the Division of Thoracic and Cardiovascular Surgery, Chang Gung Memorial Hospital, Linkou Center and Chang Gung University, College of Medicine, Taiwan. Address correspondence and reprint requests to: Dr. Po-Jen Ko, Division of Thoracic and Cardiovascular Surgery, Chang Gung Memorial Hospital, Linkou Center, 199 Tun-Hwa North Road Taipei, Taiwan 105. Tel. +886 (332) 81200. Fax: +886 (332) 85818. E-mail: huang137@mac.com

References

Isoniazid susceptibilities of Mycobacterium tuberculosis on blood agar

Cilem Yildiz, MD, Mahmut Ulger, MSci, Gonul Aslan, MD, Gurul Emekdas, PhD.

Tuberculosis (TB) is an important public health problem in both developed and developing countries. It is estimated that more than 8 million new cases of active TB occur annually and the global annual mortality is close to 2 million people. Mycobacterial cultures and susceptibility testing must be rapidly concluded for effective treatment and control of the disease. The 2 methods most commonly used for susceptibility testing of Mycobacterium tuberculosis (M. tuberculosis) include the proportion method performed on Lowenstein-Jensen medium (LJ) and Middlebrook 7H10-11 agar, and the BACTEC 460 TB system Becton Dickinson, sparks, MD, USA). The proportion method requires 3 weeks of incubation. The BACTEC 460 TB system uses a broth medium containing radio labeled palmitic acid substrate and results can be reported in 4-7 days, but it is labor-intensive, expensive, and generates radioactive waste. The incidence of multidrug-resistant tuberculosis (MDR-TB), has increased in recent years. The MDR-TB, caused by strains resistant to at least isoniazid (INH) and rifampicin (RMP), is considered an emergent disease as well as the consequence of inadequate treatment. The World Health Organization has estimated that approximately 460,000 MDR-TB cases occur each year. Early detection of MDR M. tuberculosis strains is important for control of tuberculosis. Drancourt et al.
investigated the effectiveness of blood agar for primary isolation of *M. tuberculosis*. They reported that *M. tuberculosis* can easily grow on blood agar in 1-2 weeks and that this medium has been routinely used instead of egg-based medium in the inoculation of 10,000 samples in a year for the diagnosis of tuberculosis, with the same results being obtained. The use of blood agar media for recovery of *M. tuberculosis* was reported early last century. A comparative study of different media conducted in 1977, suggested that penicillin blood agar would be at least as good as, if not better than, LJ medium for recovering *M. tuberculosis*. Blood agar is commonly preferred in many clinical microbiology laboratories as it is inexpensive and several bacteria are readily grown on it. In several studies, it has been reported that blood agar could be used for the isolation of *M. tuberculosis*. In our study, we evaluated the performance of sheep blood agar and human blood agar for susceptibility testing of *M. tuberculosis* clinical isolates to INH by using the proportion method. The proportion method was used described by the National Committee for Clinical Laboratory Standards and blood agar was used instead of Middlebrook 7H10 agar. Freshly grown colonies were transferred to a tube containing 3-4 ml of 7H9 broth and 4-5 sterile glass beads. The tubes were vigorously agitated on a vortex mixer, and then clumps were allowed to settle for 30-45 minutes. The supernatants were adjusted to equal densities of a number one McFarland standard with 7H9 broth and used as the standard inoculum for the proportion method. Each standard inoculum was diluted 100-fold with 7H9 broth. One hundred microliters of diluted inoculum was inoculated on blood agar medium with and without drugs. All plates were incubated at 37°C overnight, and then they were sealed, placed in plastic bags, and incubated at 37°C in 5-10% carbon dioxide.

The study was performed in Mersin University Research Hospital Microbiology Laboratory, between April-June 2006.

In this study, 60 clinical isolates of *M. tuberculosis* were examined, and H37Rv were included as control strains. Drug susceptibility patterns of all isolates were previously detected by the BACTEC 460 TB system (Becton Dickinson, Sparks, MD, USA) and a standard protocol in accordance with the manufacturer’s instructions was followed. In this study, 33 isolates of *M. tuberculosis* were susceptible to INH while 24 were resistant. The blood agar media image is shown in Figure 1. The study results are summarized in Table 1 and all plates were evaluated at 6, 14, and 21 days according to the growth on the control well. Our results of the susceptibility test performed on blood agar (5% sheep and human) were obtained on the 6th day of incubation for isolates, the study showed that both blood agar can be used as an alternative medium for the susceptibility testing of *M. tuberculosis*. In our study, the plates were examined in the 6th, 14th, and 21st days of incubation. On the 6th day of incubation, colonies of 45 out of 60 isolates were visible macroscopically on blood agar, but the susceptibility testing results could not be evaluated. However, on the 14th day of incubation, all results were noted but incubation was prolonged to the 21st day. By the 21st day of incubation, we did not find any significant differences in susceptibility testing, but contamination was observed in 3 isolates (5%). The results were compared with the BACTEC 460 TB method as the reference, and the agreements

<table>
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<th>Results on blood agar</th>
<th>Results on blood agar human/sheep</th>
<th>Radiometric proportion method</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
</tr>
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<tbody>
<tr>
<td>Resistant</td>
<td>100</td>
<td>24/24</td>
<td>24</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Susceptible</td>
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<td>33/33</td>
<td>36</td>
<td>92.3</td>
<td>100</td>
<td>100</td>
<td>88.8</td>
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PPV - Positive predictive value, NPV - Negative predictive value.
were determined as 100% for INH. Three isolates were contaminated so we did not include these in the final results.

Coban et al8 evaluated blood agar as an alternative medium in drug susceptibility testing of 34 clinical isolates of M. tuberculosis to INH, RIF, ethambutol (ETM), and streptomycin (STR). They reported results of both methods were 91.1%, 97% and 100% agreement for INH, STR, RIF, and ETM. In addition, their results of the susceptibility test performed on blood agar were obtained on the 14th day of incubation for 22 isolates; the study showed that blood agar can be used as an alternative medium for the susceptibility testing of M. tuberculosis. In Coban’s study, the agar proportion method was performed on sheep blood agar; however, in our study the agar proportion method was performed on both sheep and human blood agar, with a different methodology. In this study, we demonstrated that susceptibilities of M. tuberculosis were achieved within 6-8 days after inoculation of clinical isolates in both mediums. Since blood agar is not a selective medium, it may be more suitable for fastidious, slow-growing organisms. So, in our study we observed contamination on both mediums.

In conclusion, we showed that both agars used with the proportional method have similar diagnostic accuracy, however, with respect to cost, blood agar is more convenient than Middlebrook 7H10 agar and BACTEC 460.

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From the Department of Microbiology and Clinical Microbiology, Medical Faculty, Mersin University, Zeytinlibahce, Mersin, Turkey. Address correspondence and reprint requests to: Dr. Gonul Aslan, Department of Medical Faculty Microbiology and Clinical Microbiology, Mersin University, Zeytinlibahce, Mersin, Turkey. Tel: +90 (324) 3412818. E-mail: drgaslan@mersin.edu.tr

References


The role of fine needle aspiration cytology in the diagnosis of peripheral lymphadenopathy. An institutional experience of 83 cases

Hussein A. Al-Abkari, FRCIS, CABS, Sohail A. Butt, PhD, FCPS, Abdulghani E. Al-Abkari, BS, Mahmuda Ahmed, MD.

Expanded head and neck, and less commonly axillary, and inguinal lymph nodes are common clinical problems. It may be the result of a variety of different underlying diseases. History and physical examination alone are not always helpful in the evaluation of the underlying causes, so accurate tissue diagnosis is required. Lymph node fine needle aspiration cytology (FNAC) is valuable in solving the diagnostic problem of peripheral lymphadenopathy. It is a suitable alternative to the surgical excisional biopsy requiring general anesthesia. It is a simple, rapid, safe, and inexpensive technique, but its accuracy depends on the quality of the obtained specimen and on the experience of the cytologist. After complete history and physical examination, patients presenting to the surgical clinic of Dammam Central Hospital between 2002 and 2005 with peripheral lymphadenopathy, underwent FNAC. The aspirates were obtained using a 21-gauge needle with 20 ml disposable plastic syringe, smeared on at least 3 slides. The air-dried smears were stained with Diff-Quick or Giemsa, and the alcohol fixed smears with hematoxylin and eosin stain. No local anesthesia was required. Irrespective of the cytological diagnosis and after obtaining informed consent, all patients were subjected to excisional biopsy of the earlier aspirated enlarged lymph nodes under local or general anesthesia. The findings in the FNAC were correlated with the clinical data and the histological results to assess
the accuracy of FNAC in the diagnosis of peripheral lymphadenopathy.

Fine needle aspiration cytology was performed in 91 patients with peripheral lymphadenopathy. The age of patients ranged from 13-78 years with a median of 34 years. There were more females than males with a male-female ratio of 1:3. Inadequate specimens due to poor cellularity were obtained in 8 patients (8.8%), who were excluded from the study. The study was carried out on the remaining 83 patients. Most of the aspirated lymph nodes were from the head and neck in 67 patients (81%). Generalized, inguinal, and axillary lymphadenopathy was found in 9 (11%), 4 (4.5%) and 3 (3.5%) patients. Local anesthesia was used in 13 patients (15.6%). The most common definitive diagnosis was tuberculous lymphadenopathy in 31 patients, constituting 37.4%. Diagnosis of reactive hyperplasia, lymphoma, and metastatic malignancy was made in 30 (36%), 16 (19.3%) and 6 (7.3%) patients. Correct diagnosis obtained by FNAC was found in 62 patients, giving an overall diagnostic accuracy rate of 75%. As noticed from Table 1, 17 patients with tuberculosis, one with metastatic tumor, and 4 with lymphoma were diagnosed by FNAC as reactive hyperplasia. These 22 cases were considered as false negative cases. None of the patients with benign reactive hyperplasia on FNAC were subsequently found to have tuberculosis or malignant tumor. One or more of the triad of symptoms of fever, night sweating, and weight loss was found in 9 patients (30%) with reactive hyperplasia, 12 (39%) with tuberculosis, 6 (37.5%) with lymphoma, and one patient (17%) with metastatic tumor. No significant complications were encountered in all FNAC cases, but 2 patients developed wound infection after excision of cervical lymph nodes.

The utilization of lymph node fine needle aspiration (LNFNA) for diagnostic purposes dates from 1921. Subsequent studies showed that well performed LNFNA, in which the material obtained was properly handled and processed, offered a reliable, quick, safe, and cost-effective alternative to surgical excision with high diagnostic accuracy in peripheral lymphadenopathy. However, certain limitations and pitfalls have to be appreciated and the clinicians and the cytopathologists must be aware of the diagnostic limitations of this method. Reports in the literature have highlighted the difficulties in distinguishing reactive hyperplasia from low-grade lymphoma, tuberculous lymphadenopathy, and metastatic malignancy. Lioe et al\(^1\) found diagnostic difficulty in distinguishing low-grade malignant lymphoma from reactive hyperplasia in 163 fine needle aspirates. He related this difficulty to the fact that although a mixed population of lymphoid cells in an aspirate would point towards a reactive process; some cases of low grade non-Hodgkin’s lymphoma (NHL) may contain occasional plasma cells, eosinophils, and even tingible body macrophages, especially if the nodal architecture is only partially effaced. Hodgkin's disease, particularly of the lymphocyte predominant subtype, could also prove exceedingly difficult to diagnose, as characteristic Reed-Sternberg cells may be very low in numbers amidst a polymorphous background. Lau et al\(^2\) reported that FNAC examination had a sensitivity of 77% in the diagnosis of cervical tuberculous lymphadenitis and recommended the combined use of Mantoux test to increase the sensitivity of FNAC. Shaha et al\(^3\) also stated that accurate cytological interpretation may be difficult in inflammatory disease of the lymph nodes. Lymphoma and metastatic undifferentiated carcinoma may be cytologically indistinguishable. Aspiration of necrotic material from the center of metastatic lymph nodes may give false-negative results. The benign hyperplastic lymph node may be difficult to distinguish from lymphoma. The overall diagnostic accuracy of 75% and sensitivity of 60% in our review is comparable to a number of published studies. As shown in many studies, the diagnostic accuracy of FNAC may be enhanced by several factors, including on-site cellular adequacy evaluation, special histochemical and immunochemical stains, in situ hybridization, and

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<th>Histological Diagnosis</th>
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The role of FNAC in the diagnosis of peripheral lymphadenopathy

In conclusion, FNAC therefore proves to be a useful (screening) procedure by selecting out those patients who would require further assessment including surgical biopsy. However, due to its limitations, it does not totally replace surgical biopsy in the investigation of peripheral lymphadenopathy.

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From the Department of Surgery (Al-Abkari), Dammam Central Hospital, and the Regional Laboratory and Blood Bank (Butt, Al-Abkari, Ahmed), Dammam, Eastern Province, Kingdom of Saudi Arabia. Address correspondence and reprint requests to: Dr. Hussein A. Al-Abkari, PO Box 60535, Qatif 31911, Kingdom of Saudi Arabia. Tel. +966 5005800870. Fax. +966 (3) 8155618. E-mail: huabkari@hotmail.com

A life-sustaining single dose of recombinant activated factor VII for an Egyptian patient with hemorrhagic crisis

Gamal Badra, MD, Mohamed El-Abassy, MD, Mahmoud Loffy, PhD, Faris Q. Alenzi, PhD, Imam Waked, MD.

Bleeding is a well-known complication of anticoagulant treatment. The annual incidence of major hemorrhages with, for example, vitamin K antagonists has been reported to vary between 2-7%. This incidence is 2-3-fold higher for minor bleeds.1 For a one-week course of intravenous heparin therapy, the major bleeding rate is approximately 1–3%.1 When such a serious bleeding episode occurs, the use of a specific antidote is an option. There are 3 main types

References


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Recombinant activated factor VII in hemorrhagic
diseases

A 30-year-old male was admitted to the National Liver Institute (NLI), Minufiya University with persistent hematemesis, and hemoptysis with melena 6 hours before admission. The bleeding was precipitated by a large dose of non-steroidal anti-inflammatory drugs (NSAID) as oral diclofenac for his right arm fracture in an accident. He was using both warfarin and digitalis due to a mitral valve replacement 5 years ago. On admission, the blood pressure was 100/60, pulse 170, and temperature 38°C. The abdomen showed no localized or generalized tenderness, no splenomegaly, and the liver was not palpable. The electrocardiogram (ECG) showed rapid arterial fibrillation (AF), heart rate was 190/min. The laboratory investigations were found normal except the hemoglobin and prothrombin rate was 190/min. The laboratory investigations were normal except the hemoglobin and prothrombin rate was 190/min.

Life-threatening bleeding occurs when an acute hemorrhage is massive and uncontrollable with the patient receiving numerous transfusions in a short period. Massive loss of blood can also lead to a clotting impairment of the remaining blood. There are many underlying causes of clinically significant blood loss including trauma, surgery, and postpartum hemorrhages. Recombinant activated factor VII (NovoSeven; Novo Nordisk, Denmark) has been recommended as a therapy of last resort to controlling life-threatening bleeding in a patient with mitral valve replacement.

The abdominal ultrasound showed the liver of normal size with perportal fibrosis, normal sized spleen (10 cm) and no ascites. The first treatment included intravenous vitamin K, omeprazole, 2 packs of red blood cells (RBCs), and 4 units of fresh-frozen plasma. Moreover, he received digoxin 0.25 ug, amiodarone HCl 200 mg/day, and cefotaxime one gm/6 hours. After extensive blood product support failed to control hemorrhage, he was transferred to the intensive care unit (ICU) and received a single dose of activated factor VIIa (90 ug/kg) in combination with amiodarone and digitalis. Commercially available rFVIIa, (Novo-Seven, Novo Nordisk, Denmark) was used. After administration, the bleeding settled dramatically and eventually ceased. Six hours later, the heart rate reached 90/min. One day later, an obvious recovery was obtained and the international normalized ratio (INR) value shifted to 2.2. Upper gastrointestinal endoscopy revealed non-bleeding multiple gastric and duodenal erosions. After improvement of his general condition, he was discharged with his medications to control the broncho-pneumonia and gastrointestinal tract erosions.

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Table 1 - Laboratory data obtained for the patient with bleeding.

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (gm/dl)</td>
<td>8</td>
<td>12-16</td>
</tr>
<tr>
<td>Platelets (µ x 10⁹)</td>
<td>409</td>
<td>150-450</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.1</td>
<td>up to 1.4</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.2</td>
<td>up to 1</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dl)</td>
<td>0.4</td>
<td>up to 0.25</td>
</tr>
<tr>
<td>Total protein (gm/dl)</td>
<td>6.5</td>
<td>6-8.5</td>
</tr>
<tr>
<td>Serum albumin (gm/dl)</td>
<td>3.7</td>
<td>3.5-5</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/I)</td>
<td>29</td>
<td>up to 45</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/I)</td>
<td>27</td>
<td>up to 40</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/I)</td>
<td>60</td>
<td>21-92</td>
</tr>
<tr>
<td>Gamma glutamyl-transferase (U/I)</td>
<td>34</td>
<td>up to 49</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>7</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>Activated partial thromboplastin time</td>
<td>32</td>
<td>24-40</td>
</tr>
<tr>
<td>Fibrin degradation product (µg/ml)</td>
<td>5</td>
<td>&lt;10</td>
</tr>
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</table>
Recombinant activated factor VII in hemorrhagic

attain hemostasis in difficult clinical situations. The successful administration of recombinant activated factor VII has been reported in patients with severe trauma and those undergoing cardiac and abdominal surgery, in which the drug represents an effective and well-tolerated treatment for serious bleeding episodes during both surgery and postoperatively. The results of standard coagulation tests in our patient were remarkable, with abnormal prothrombin time but normal platelet count. Thus, a factor VII deficiency was included as a cause of bleeding. Factor VII deficiency should be suspected if only the prothrombin time is prolonged while other tests such as activated partial prothrombin time, thrombin time, and platelet count are normal. Continuous bleeding led to a decrease in prothrombin time and platelet counts, although prothrombin complex concentrates, and fresh-frozen plasma were substituted. Changes in the hemostatic system are known to occur in patients who have experienced heavy blood loss and have received multiple blood transfusions. Those patients can experience impaired thrombin generation, which results in a less stabilized fibrin hemostatic plug that is very sensitive to fibrinolytic activity. Exogenous recombinant activated factor VII induces thrombin generation due to saturation of all tissue factor sites with activated factor VII at the site of injury, and it generates thrombin on the activated platelet surface. Thus, the thrombin-generating effect of recombinant activated factor VII was shown to be tissue factor-dependent (activation of factors IX and X by a complex of activated factor VII and tissue factor) and tissue factor-independent (by activation of factor X on activated platelets). Furthermore, at a lower platelet count, the initial activation was demonstrated to be enhanced after the addition of recombinant activated factor VII in a concentration-dependent manner, indicating that this clotting factor may compensate for a lower platelet count with regard to thrombin generation. By exploiting the binding capacity of activated factor VII to platelets, recombinant activated factor VII is able to increase the capability of the hemostatic system, which is not achieved by administration of fresh-frozen plasma and prothrombin complex concentrates alone.

In conclusion, this report demonstrates the beneficial effect of recombinant factor VIIa (rFVIIa) in controlling life-threatening hematemesis and hemoptysis in a patient treated for long time with anticoagulants due to mitral valve replacement. Therefore, treatment of hemorrhage with rFVIIa reduces mortality, and improves outcomes in those cases. This makes recombinant activated factor VII useful as an additional hemostatic agent in very difficult bleeding situations after failure of conventional measures to achieve hemostasis.

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From the Department of Hepatology (Badra, El-Abasy, Waked), Department of Molecular and Cellular Biology (Lotfy), Minufiya University, Sadat City, Minufiya, Egypt, and the Department of Medical Laboratory Sciences (Alenzi), College of Applied Medical Sciences, King Faisal University, Dammam, Kingdom of Saudi Arabia. Address correspondence and reprint requests to: Dr. Gamal Badra, Department of Hepatology, National Liver Institute, Minufiya University, Minufiya, Egypt. E-mail: mlotfy2000@yahoo.com

References