รายงานผู้ป่วย

Pulmonary calcification after liver transplantation: A case report

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Keelawat S, Chongsrisawat V, Rungruxsirivorn S, Suwangool P, Chomdej S, Nivatvongs S, Karnsawai S, Poovorawan S. Pulmonary calcification after liver transplantation: A case report. Chula Med J 1999 Aug; 43(8): 569-76

We report here the case of a 5 11/12 year-old girl with extrahepatic biliary atresia who developed pulmonary calcification after orthotopic liver transplantation. She required multiple intra- and post-operative blood transfusions. Previous reports of soft tissue calcification following liver transplantation were reviewed. The potential pathogenesis of pulmonary calcification in this patient was metastatic calcification whereas the cause issuing from dystrophic calcification could not be concluded because there was no firm evidence that this patient had pneumonia or any kind of lung injuries prior to the development of this pulmonary abnormality.

Pulmonary calcification is usually benign and may not require specific treatment. However, this condition may be potentially progressive and cause fatal respiratory failure. Therefore, preventing its development is crucial.

Key words: *Pulmonary calcification, Liver transplantation.*

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Received for publication. June 10, 1999.

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รายงานผู้ป่วยเด็กผู้หญิง อายุ 5 ปี 11 เดือน ซึ่งเป็นโรค extrahepatic biliary atresia ผู้ป่วยรายนี้ได้รับการปลูกถ่ายตับแล้วต่อมาภายหลังมีหินปูนมาเกาะในเนื้อปอด ผู้ป่วยได้รับการถ่ายเลือดหลายครั้งระหว่างและหลังจากการผ่าตัดปลูกถ่ายตับ คณะผู้รายงานได้ทบทวนวรรณกรรมเรื่องภาวะหินปูนจับในเนื้อเยื่อในที่ต่าง ๆ ของร่างกายภายหลังได้รับการปลูกถ่ายตับ สำหรับภาวะหินปูนเกาะในเนื้อปอดของผู้ป่วยรายนี้ผู้รายงานเชื่อว่าสาเหตุมาจาก metastatic calcification ส่วนสาเหตุจาก dystrophic calcification ไม่สามารถสรุปได้เพราะว่าไม่มีหลักฐานเพียงพอที่จะชี้ว่าผู้ป่วยเคยมีปอดอักเสบหรือภาวะอื่น ๆ ที่ทำให้มีการบาดเจ็บต่อเนื้อเยื่อปอดมาก่อนที่จะเกิดรอยโรคนี้ขึ้น

โดยทั่วไปภาวะหินปูนเกาะในเนื้อปอดนี้มักไม่ก่อให้เกิดอันตรายต่อผู้ป่วยและอาจไม่ต้องทำการรักษาใด ๆ อย่างไรก็ตาม ในบางรายอาจทำให้เกิดอาการรุนแรงจนถึงขั้นเกิดอาการหายใจล้มเหลวได้ ดังนั้นการป้องกันการเกิดภาวะนี้จึงเป็นสิ่งสำคัญ

Liver transplantation is associated with many complications, as for example, surgery-related hepatic complications, or those caused by immunosuppressive therapy. One such complication is ectopic soft tissue calcium deposition at various sites of the body.[1,2] Among all the different organs, the lungs are most frequently affected.[1,2] A case of a 5-year, 11-month-old girl who underwent liver transplantation and developed pulmonary calcification is reported, accompanied by a review of the available literature in order to propose the pathogenesis of this complication.

Case Report

A 5 - year, 11 – month - old girl, a known case of biliary atresia, had undergone a Kasai procedure at 3 months of age. After the operation, she still had persistent jaundice and developed secondary biliary cirrhosis. Liver transplantation was performed twice, at 5 years, and 5 years, 3 months of age, respectively. The preoperative chest radiogram was unremarkable.

The total amounts of blood products transfused during the first operation and within one month thereafter were quite large. Altogether, she required transfusion of 3,970 ml of fresh frozen plasma, 3,382 ml of packed red cells, 2,465 ml of platelets, 275ml of cryoprecipitate and 3,200 ml of whole blood.

Three - hundred milligrams intravenous calcium were administered during surgery and additional 2 grams were given one day after the transplantation. Hypocalcemia, however, developed for 2 days postoperatively (minimum serum calcium = 5.5mg/dl) and hyperphosphatemia was also evident for 7 days after the surgery (maximum serum phosphate = 7.9mg/dl).

The patient was on a mechanical ventilator for 9 days after the operation. The chest radiogram showed bilateral pleural effusion 4 days after the first transplantation. Intercostal drainage was performed on the right side and the right pleural effusion was decreased.

As the first transplantation was complicated by hepatic artery thrombosis and her liver function deteriorated, a second operation was performed.

During the interval between the first and second transplantation, chest radiograms revealed pleural effusion of varying intensity, at times completely subsiding, which was found more pronounced on the right side and was improved by albumin and diuretics administration.

For the second operation, the patient required transfusion of 2,540 ml of fresh frozen plasma, 2,920 ml of packed red cells, 410 ml of platelets and 150 ml of cryoprecipitate during surgery and within one month thereafter. Also, 300 mg intravenous calcium were given intraoperatively and 4 grams within 48 hours after surgery.

Similarly, hypocalcemia and hyperphosphatemia also developed as noted in the first operation (minimum serum calcium = 6.5 mg/dl, maximum serum phosphate = 7.9mg/dl). At this occasion, however, the conditions were transient and remained for only one day after the transplantation.

Following the second operation, she needed the ventilator for a shorter duration (2 days). A bacterial culture started from endotracheal secretion yielded Pseudomonas aeruginosa growth.

The chest radiogram showed small right pleural effusion and course reticular infiltration of both lower lungs 4 days after the second operation. The follow-up chest X-ray remained unchanged 8 days after the surgery although antibiotics had been given.

After the second surgery, jaundice still persisted. Therefore, ultrasonography was performed three months after the transfusion and it revealed mild stenosis of the hepatic vein just before its drainage into the inferior vena cava. The angiogram showed total occlusion of the hepatic artery but the portal vein was patent. Liver biopsy disclosed intrahepatic cholestasis. No evidence of rejection was detected. She was kept under immunosuppressive therapy with a regimen of cyclosporin A, prednisolone and azathioprine.

Four months after the second transplantation, the patient was admitted due to fever, cough and fatigue. The chest radiogram disclosed dense course reticulonodular patterns of infiltration in both lower lungs. Sputum culture revealed growth of Klebsiella species. The clinical impression was pneumonia. The follow-up chest X-ray 4 days after admission remained unchanged. The condition improved after antibiotics were given and she was discharged.

Six months after the second transplantation, she was admitted due to high-grade fever, abdominal pain and drowsiness. She died one day after admission. The cause of death was septicemia. The chest radiogram performed at this admission was identical to the previous one obtained four months post transplantation.

Before, as well as after either transplantation, she had not suffered from renal insufficiency. The immunosuppressive drugs administered for prevention of rejection were cyclosporin A, azathioprine and prednisolone.

Autopsy findings showed cellular rejection of allografts with marked fibrosis at the porta hepatis. There were diffused calcified deposits in the alveolar septae, in both lower lungs. These calcium crystals were stained with Von Kossa for confirmation. No

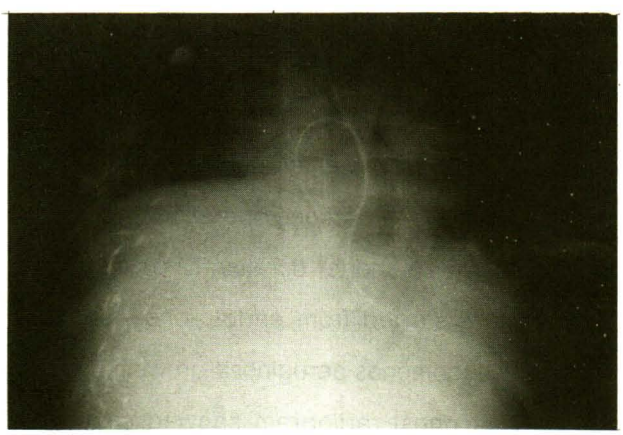

Figure 1. Chest radiogram on the 4th day following the first transplantation, showing bilateral pleural effusion.

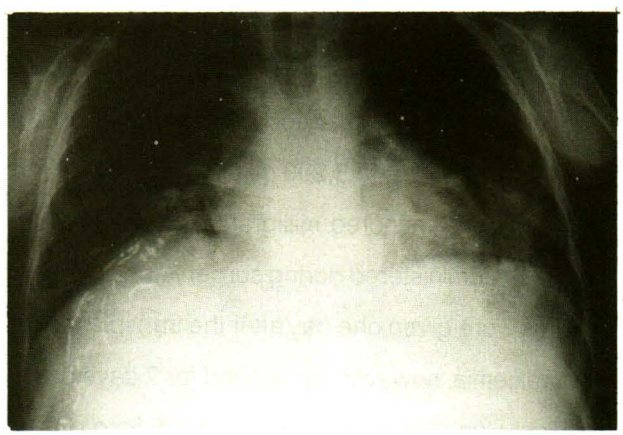

Figure 2. Chest radiogram, 4 months after the second transplantation, showing dense course reticulonodular patterns of infiltration in both lower lungs.

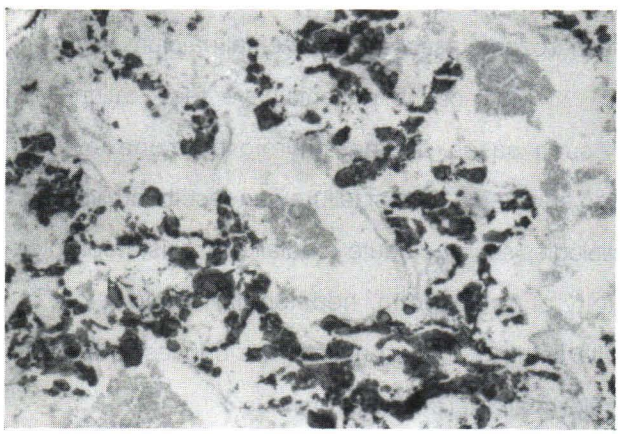

Figure 3. Low magnification of lung tissue showing diffuse calcification in the alveolar septae.

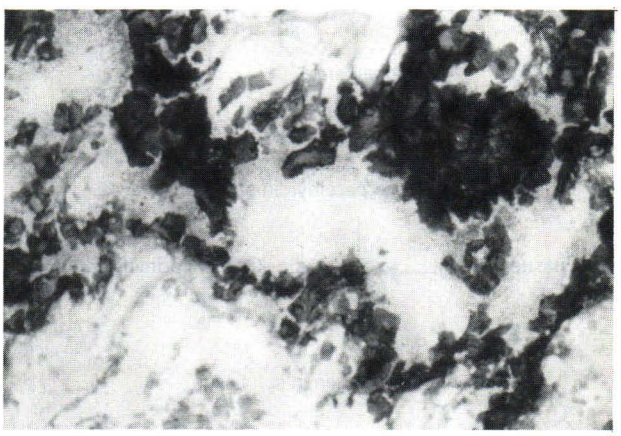

Figure 4. High magnification of calcium deposits in the alveolar septae.

evidence of pneumonia was detected. Organizing and acute peritonitis with pyoperitoneum and evidence of disseminated intravascular coagulopathy were found. These findings were compatible with clinical septicemia.

Discussion

Soft tissue calcification after liver transplantation has been described in the medical literature. Several studies have been conducted in order to elucidate its pathogenesis. Munoz et al [1] investigated 20 patients who had undergone liver transplantation due to different causes and they discovered 7 cases (47%) developing ectopic calcium deposition in various organs. Wachtel et al [2] did similar work and found that 21 of a total of 25 cases (84%) had tissue calcification. Libson et al [3] reviewed chest radiograms of 77 patients after liver transplantation and found pulmonary calcinosis in four. Jensen and associates [4] evaluated pulmonary complications following liver transplantation in 18 individuals and found two of them developed pulmonary calcification. Although this condition appears to be detected to a high degree in some studies, to our knowledge, no case has been reported in Thailand.

Generally, there are two distinct pathogenic mechanisms leading to calcification, metastatic and dystrophic. [1,5,6] Metastatic calcification is caused by hypercalcemia and can occur in normal tissues while dystrophic calcification occurs in damaged tissues with normal circulating levels of calcium and phosphate. [1,5,6] The most common cause for metastatic calcification is hypercalcemia due to renal failure with secondary hyperparathyroidism. [5,7] Dystrophic pulmonary calcification may occur in damaged lung tissue after infection, infarction or haemorrhage. [5]

Munoz and coworkers [1] suggested the pathogenesis of ectopic soft tissue deposition following liver transplantation to be multifactorial.

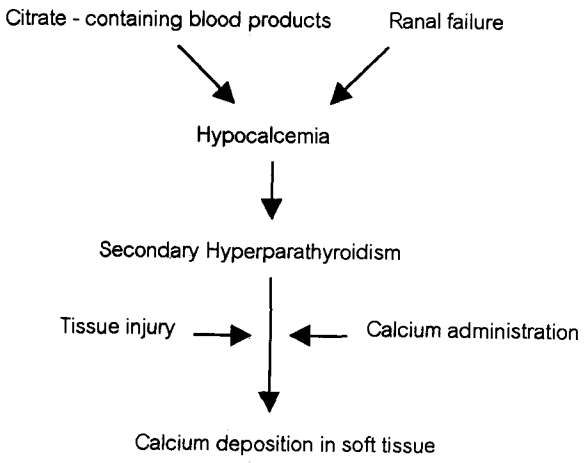

Figure 5. Possible pathogenetic factors in ectopic soft tissue calcium deposition following OLT.

Transfusions of large amounts of citrate-containing blood products, particularly fresh frozen plasma, associated with renal failure results in sustained hypocalcemia which in turn stimulates the secretion of parathyroid hormone. Mobilization of calcium from bone and exogenous calcium administration result in cellular calcium deposition if tissue injury, or local factors as yet unidentified, are simultaneously present. This hypothesis can be graphically summarized as demonstrated below.

Citrate in blood products causes hypocalcemia by binding to calcium. [8,9] A study on citric acid intoxication by Bunker and associates[10] reported that very high concentrations of serum citrate were observed during multiple transfusions in patients with either liver disease or mechanical obstruction to hepatic circulation since, as a result of hepatic dysfunction, the citrate received is only poorly metabolized. [4] Hence, severe depression of serum ionized calcium occurs. According to Munoz et al, patients who developed soft tissue calcification required significantly more packed red blood cells, citrated fresh frozen plasma and elemental calcium. [1]

Most of the patients have renal failure. [1,2] In such cases, the parathyroid hormone level is also elevated. [1] Renal failure can result from various etiologies such as acute tubular necrosis, nephrotoxicity of cyclosporin, hepatorenal failure etc.[11,12] With some of these patients, the causes to explain their renal failure are not obvious. [11]

Changes in the acid-base status may also play a role in the development of calcification since the solubility of calcium phosphate is inversely proportional to the pH. [1] The high frequency of calcium deposits observed in lungs may in part be related to the increased pH in perialveolar tissues. [1] Similarly, due to the increased generation of bicarbonate, calcium deposits may readily form in the gastric mucosa and kidneys. [1]

Pulmonary calcification may lead to respiratory insufficiency, [1,2,4,5] although some patients remain asymptomatic. [1,5] Moreover, soft tissue calcification following liver transplantation may be associated with osteoporosis and bone fractures. [1]

In the case reported here, several factors might have led to the development of soft tissue calcification. These included large amounts of blood products transfused during and after the transplantation, intravenous calcium administration intra - and postoperatively. These events can lead to metastatic calcification. Moreover, the use of a mechanical ventilator might have played a role in this patient since it could alter the pH in the lungs. Repeated transplantation as with this patient may increase the risk of this rather rare condition. According to the studies

performed by Munoz and colleagues, [1] four of the seven patients who developed soft tissue calcification had undergone re-transplantation. With this patient, chest radiograms indicated that calcification might have started to develop already 4 days after the second transplantation.

Since there was no evidence of pneumonia based on chest x-rays but nevertheless, it was suspected based on the clinical manifestations alone, the role of dystrophic calcification could not be excluded.

Regarding prevention and treatment, preoperative assessment of parathyroid hormone levels and vitamin D status will identify individuals with either abnormal parathyroid status or vitamin D deficiency. Correction of vitamin D levels before surgery should be attempted. Use of blood products, especially fresh frozen plasma, should be minimized as should exogenous calcium administration. If renal failure develops, dietary reduction of phosphate intake and use of phosphate binding antacids should be considered. [1,13] In a case reported by Munoz et al, [1] correction of the vitamin D level by giving calcitriol (0.5 microgram b.i.d.) reduced dyspnea of the patient who had pulmonary calcification following liver transplantation. In the study of Jensen and colleagues, [4] one of two cases who developed pulmonary calcification was treated with mithramycin and calcitonin.

Summary

A case of pulmonary calcification following liver transplantation is described. This condition is found in high proportion in some studies and it can occur in many organs in the body. The factors responsible for the development of metastatic calcification include renal failure, citrate-containing blood products, hyperparathyroidism, acid-base changes and calcium administration during and following surgery. Both metastatic and dystrophic calcifications may account for the pathogenesis.

Finally, since the lung is one of the more common sites for this to occur, one should add this condition to the list of differential diagnoses if pulmonary infiltration detected during the postoperative course following liver transplantation does not resolve with appropriate antibiotic treatment.

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