supplement to qualitative interpretation of scintiscans, pulmonary perfusion scintigraphy will become a more useful technique for clinical evaluation of treatment and assessment of breathlessness and respiratory failure than the usual one.

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Lymphoscintigraphy and Lymphangiography of Lymphangiectasia

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Chronic genital edema secondary to lymphangiectasia and chylous reflux in a 23-yr-old man with Noonan syndrome was investigated by ^{99m}Tc sulfur nanocolloid lymphoscintigraphy and bipedal contrast lymphangiography. Lymphoscintigraphy showed a delayed lymphatic flow pattern in the pelvis, abdomen and chest consistent with lymphangiectasia and abnormal lymphatic flow dynamics. Lymphangiography showed dilated and tortuous abnormal lymphatics in the abdomen and pelvis. Ligation of incompetent retroperitoneal lymph vessels and lymphaticovenous anastamosis were performed, resulting in clinical improvement. Lymphangiectasia has been described previously in Noonan syndrome, but it is relatively uncommon below the diaphragm. This case demonstrates the use of lymphoscintigraphy and lymphangiography in providing important physiological and anatomical information before surgical intervention. Careful presurgical planning using such tests also allows the most appropriate operation to be performed.

Key Words: Noonan syndrome; lymphangiectasia; lymphoscintigraphy; lymphangiography

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Noonan syndrome is characterized by wide-ranging phenotypic features, many of which are also seen in Turner's syndrome (*1,2*). The more common congenital cardiovascular abnormalities include pulmonary valvular stenosis, hypertrophic cardiomyopathy and atrial septal defect; however, abnormalities of the lymphatic system are also well recognized (*3–7*). In some patients, peripheral lymphoscintigraphy may be helpful in distinguishing primary lymphedema from secondary lymphedema and further evaluating congenital lymphatic abnormalities (*8*). Peripheral lymphoscintigraphy demonstrates normal or abnormal lymphatic transport of radiolabeled nanocolloid in patterns that may be diagnostic, but it more often provides additional information confirming or refuting the clinical diagnosis. Accurate anatomical detail is not, however, provided by lymphoscintigraphy and, under some circumstances, when lymphatic surgery is planned lymphangiography may also be helpful. We describe a patient with retroperitoneal lymphangiectasia in whom lymphoscintigraphy and lymphangiography were complementary in planning lymphatic surgery.

CASE REPORT

A 23-yr-old man with a sporadic form of Noonan syndrome characterized by slightly wide-spaced eyes and low-set ears, mild pectus excavatum, previous surgically corrected right cryptorchidism and moderate pulmonary stenosis/regurgitation presented with a 7-yr history of genital edema and chronic painless eruption of scrotal vesicles associated with fluid

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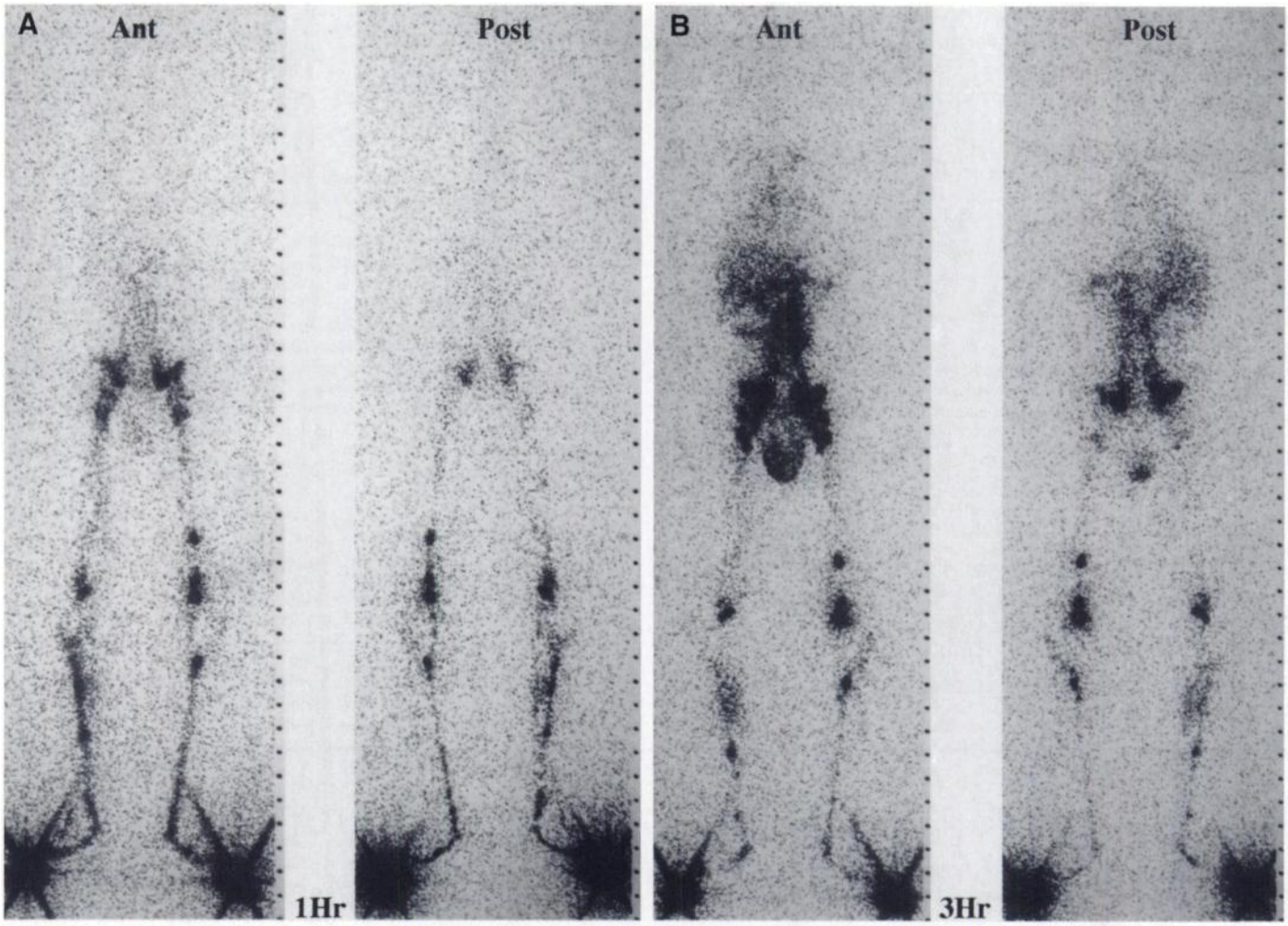

FIGURE 1. (A) Lymphoscintigraphy at 1 hr shows radiotracer at injection sites in both feet and relatively symmetrical, rapid radiotracer uptake in inguinal regions bilaterally. Mild diffusely abnormal radiotracer distribution is seen in pelvis and scrotum consistent with lymphangiectasia. In addition, unusual pattern of multiple discrete lymph nodes seen along lymphatic channels of lower extremities is of uncertain significance. No radiotracer activity is seen in liver, indicating delayed flow of lymph from dilated pelvic and thoracic lymphatic channels into venous circulation. (B) Lymphoscintigraphy at 3 hr shows avid radiotracer uptake in iliac lymphatics, and refluxing radiotracer is seen in scrotum, perineum, retroperitoneal and very likely in mesenteric lymph vessels. More diffuse radiotracer uptake is seen in central abdomen and thorax consistent with lymphangiectasia. Liver is now visualized, indicating free passage of radiotracer from lymphatics into systemic circulation. Persistent uptake of radiotracer is seen in unusual pattern of lymph nodes in lower extremities.

leaking from the scrotal skin surface. Physical examination revealed erythema and skin thickening of the scrotum. In addition, there were multiple scrotal vesicles that discharged a whitish fluid. MRI performed 3 yr earlier showed diffuse lymphangiectasia in the pelvis extending bilaterally into the scrotum and superiorly in the retroperitoneum into the paraaortic region. No abdominal or pelvic lesions were detected. Technetium-99m filtered sulfur colloid lymphoscintigraphy showed extensive lymphatic abnormalities, which included abnormal lymphatic flow into the thorax. Reflux of the radiotracer into the scrotum confirmed incompetence of the pelvic lymphatics. In addition, radiotracer flow to the systemic circulation, as indicated by hepatic uptake, was delayed and consistent with a reduced lymphatic flow rate (Fig. 1). Lymphangiectasia was confirmed by bipedal contrast lymphangiography, which showed no normal lymphatic anatomy above the inguinal ligament and multiple dilated lymphatic collateral vessels throughout the abdomen (Fig. 2). A clinical diagnosis was made of severe retroperitoneal lymphangiectasia with reflux of chyle to the perineum, scrotum and penis.

Before Stage 1 surgery, the patient ingested 60 mg butter and 110 g cream which, at the time of surgery, demonstrated the dilated refluxing retroperitoneal lymphatics. All refluxing dilated retroperitoneal lymphatics in the region of the aortic bifurcation were ligated. A microscopically guided end-to-end lymphovenous anastomosis between a large retroperitoneal lymphatic vessel and one of the smaller mesenteric veins was performed. Excellent lymphatic flow was seen through the anastamosis. Despite very high lymphatic pressures, there was no evidence of a leak. The patient made a good recovery, and he reported reduced scrotal swelling and vesicular discharge. Stage 2 surgery (contralateral) was planned if the clinical features worsened.

DISCUSSION

This report demonstrates the importance of careful planning for corrective surgery so that an appropriate surgical procedure can be tailored to the patient's needs. In this patient, the anatomical abnormalities were defined both by MRI and lymphangiography, and the physiological abnormalities were defined by lymphoscintigraphy. The data provided by these procedures had the potential for reducing operative risk and reducing the operation's length.

Chylous reflux of the external genitalia is commonly associated with lower extremity lymphedema (*9*). Similar clinical findings to those described in this report have been published for other patients, and the chylous discharge may be precipitated by minor trauma or friction from clothing (*10,11*).

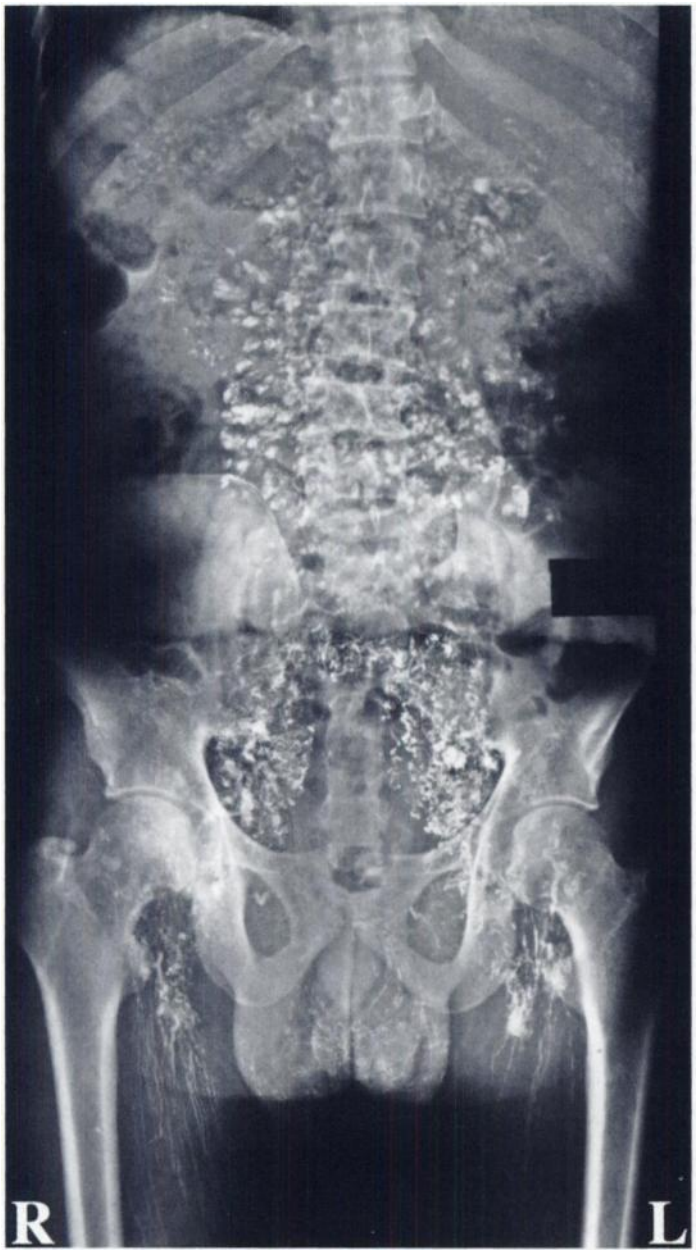

FIGURE 2. Bipedal lymphangiogram (anterior view 3 hr postinjection) shows radiographic contrast medium within deep lymphatic system of patient's lower chest, abdomen, pelvis and proximal lower extremities. Lymphatic vessels of abdomen and pelvis are aberrant, showing dilatation, tortuosity and collateral formation around para-aortic lymphatic chain.

Chylothorax is an unusual, but widely reported, lymphatic abnormality in Noonan syndrome, which is presumed to be secondary to pulmonary lymphangiectasia (*12–15*). Chylothorax may occur due to trauma, malignancy, filariasis, venous thrombosis, the rare condition, which is secondary to malignant angioma, known as massive osteolysis (disappearing bone disease) or primary lymphatic disorders involving the thoracic duct (*16*). In addition, chylothorax may occur secondary to chylous ascites in patients with primary lymphatic disorders and a normal thoracic duct (*9*). In the patient described in this report, abnormal thoracic lymphatic flow demonstrated on lymphoscintigraphy that most likely represented mild intrathoracic lymphangiectasia rather than chylothorax. Delayed visualization of the liver at 3 hr is, however, suggestive of a mild abnormality involving the thoracic duct. Lymphoscintigraphy has been shown previously to be helpful by demonstrating that thoracic/pulmonary lymphangiectasia and surgical correction (such as lymphoazygos anastomosis or peritoneovenous shunting) may be required for such patients (*9,12,17*). One patient has been described, however, in whom surgery, pleurodesis, pleurectomy and dietary fat restriction failed to correct the problem, and a clinical response was seen only after high-dose prednisone treatment (*18*).

It has been postulated that the excess nuchal skin-fold thickening seen in Noonan syndrome may be due to obstruction between the cervical and jugular lymphatic channels, which results in cystic hygroma formation that may resolve in utero (*19*). Localized lymphangiectasia and peripheral lymphedema also have been described in Noonan syndrome, and it has been postulated that some of the characteristic phenotypic features, such as webbing of the neck and anteversion of the auricles, may be secondary to transient localized lymphedema in utero (*20–25*). From the literature, it would appear that persisting lymphatic abnormalities occur sporadically in Noonan syndrome (*3,26*). It is possible, however, that lymphatic abnormalities are both more common and ubiquitous in Noonan syndrome and are only detected clinically if they are severe.

The diversity of lymphatic abnormalities that have been documented in Noonan syndrome demonstrate the need for accurate preoperative planning. Several operations can be performed for primary chylous disorders including radical excision and ligation of incompetent lymph vessels, oversewing the site of lymphatic leak, reconstructive surgery and anastamosis procedures (*27*). Consequently, accurate anatomical and physiological information is required to supplement the other clinical data before selection of the most appropriate operation. Lymphoscintigraphy is safe, easily performed and relatively noninvasive. By contrast, lymphangiography is time-consuming, invasive and not without risk of lymphangitis, pulmonary embolus and, under some circumstances, cerebral embolization and anaphylactoid reactions to the iodine-containing contrast medium (*28*). This diagnostic test, however, does have a place in the preoperative evaluation of patients undergoing surgery for primary chylous disorders and, when expertly performed, complements the data provided by lymphoscintigraphy.

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Rat Antigen-Induced Arthritis: Cartilage Alterations Assessed with Iodine-123-Antileukoproteinase

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Imaging of cartilage alterations was attempted in joints of rats with chronic antigen-induced arthritis (AIA) using the cationic ^{123}I-labeled serine proteinase inhibitor antileukoproteinase (^{123}I-ALP; pI > 10), which selectively accumulates in normal cartilage, presumably through interaction with negatively charged proteoglycans. **Methods:** Iodine-123-ALP or ^{123}I-myoglobin, a control protein of comparable size but with different isoelectric point (pI = 7.3) was injected intravenously into normal or AIA rats. Joint accumulation was followed by scintigraphy for 14 hr. Tissue radioactivity was assessed by well-counter measurements after dissection. The content of charged molecules in articular cartilage was determined by toluidine blue staining; the degree of joint destruction was assessed in parallel by x-ray, ex vivo MRI and histopathology. **Results:** In intact articular cartilage, ALP accumulated to a significantly higher degree than myoglobin. This preferential accumulation was lost in rats with chronic AIA. The target-to-background ratio for ^{123}I-ALP negatively correlated with the loss of toluidine blue staining in cartilage, which documents depletion of charged matrix molecules ($r = -0.92$, $p < 0.01$ at 4 hr; $r = -0.97$, $p < 0.01$ at 13 hr). ALP scintigraphy was sensitive in detecting cartilage alterations, even though the degree of joint destruction and inflammatory infiltration was mild, as demonstrated by x-ray, MRI and histopathology. **Conclusion:** In rat AIA, loss of ALP accumulation appears to document proteoglycan depletion in mildly altered arthritic cartilage. ALP scintigraphy may represent a functional assay for early, premorphological cartilage alterations in human arthritis as well.

Key Words: scintigraphy; x-ray; MRI; iodine-123; antileukoproteinase

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Proteolytic degradation of proteoglycans and collagens in cartilage matrix is a common feature of degenerative and chronic inflammatory joint diseases (*1*). In these disorders a disturbance of the balance between tissue-degrading enzymes, such as metallo- and serine proteinases, and their inhibitors may contribute to increased cartilage matrix catabolism (*2,3*).

Recently, an 11-kDa serine proteinase inhibitor was isolated from human articular cartilage (*4*) and identified as antileukoproteinase (ALP) (5). Interestingly, ALP expression in resident joint cells is below the detection limit of immunohistology and in situ hybridization (*6*), and no unequivocal ALP synthesis by chondrocytes can be demonstrated after biosynthetic labeling in vitro. It is, therefore, likely that ALP is produced at extra-articular sites such as the mucosa of bronchi and urogenital tract, as well as salivary and lacrimal glands (*7–10*), from which it is transferred into synovial fluid through the circulation (*11*). Indeed, the cationic molecule ALP (pI > 10) selectively accumulates in the joints of normal animals (*12*). Within individual joint structures, this accumulation is highly selective for articular cartilage, as shown by immunoprecipitation assays (*12*). Such entrapment most likely results from charge interactions with negatively charged proteoglycans.

Thus, serum-derived inhibitor molecules such as ALP, which physiologically accumulate in normal cartilage, can be exploited as targeting molecules for scintigraphic revelation of biochemical alterations in arthritic cartilage, for example, the loss of proteoglycans (*13*). This is of particular interest in view of the fact that conventional imaging techniques used in clinical routine, such as radiography or even MRI, document morphological abnormalities of cartilage only at stages in which damage is already fairly advanced and mostly irreversible (*14–16*).

Therefore, ^{123}I-labeled serine proteinase inhibitor ALP (^{123}I-ALP) was injected intravenously into rats with experimental antigen-induced arthritis (AIA). Its accumulation in cartilage was monitored by gamma camera imaging and well-counter measurements of tissue specimens. AIA was chosen because it is a chronic model of arthritis characterized by relatively slow joint destruction and low-grade chronic inflammation (*17*). This minimizes the influence of nonspecific accumulation of proteins due to increased endothelial permeability.

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