Sclerotherapy of Abdominal Lymphatic Malformations with Doxycycline

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ABSTRACT

Purpose: To assess the safety and efficacy of percutaneous image-guided sclerotherapy with doxycycline as primary treatment of intraabdominal lymphatic malformations (LMs).

Materials and Methods: Retrospective review was performed of all cases of abdominal, mesenteric, or retroperitoneal LMs referred to a single center that were subsequently treated with image-guided percutaneous sclerotherapy.

Results: Ten patients were included, of whom six were male. The mean age was 13 years (range, 2–28 y). Preprocedural cross-sectional imaging demonstrated a macrocystic malformation in nine patients and a mixed macrocystic/microcystic malformation in one. The malformation was accessed under sonographic guidance, followed by injection of opacified sclerosant agent under fluoroscopic guidance. A drainage catheter was placed in eight cases, in which sclerotherapy was repeated through the catheter for another 1 day (n = 2) or 2 days (n = 6). Doxycycline was reconstituted at 10 mg/mL, with a mean per-session dose of 608 mg (range, 80–1,000 mg) and a mean total dose of 1,230 mg (range, 80–3,000 mg). Peritoneal spill was identified in one case, but the patient remained asymptomatic. No other complications were encountered. Follow-up imaging was available in eight patients: complete resolution was seen in seven, with partial resolution in one. There was no recurrence of clinical symptoms in the follow-up period.

Conclusions: Initial results indicate that percutaneous image-guided sclerotherapy of macrocystic intraabdominal LMs with doxycycline is a safe and effective procedure.

ABBREVIATION

LM = lymphatic malformation

Lymphatic malformations (LMs) are congenital vascular anomalies that result from abnormal development of the lymphatic channels (1). The lesions may be classified as macrocystic, microcystic, or combined. The vast majority of LMs occur in the head and neck region (2), with the abdomen a rare site of involvement. Abdominal LMs are most commonly macrocystic, involve the mesentery and retroperitoneum, and, in contrast to other mesenteric cysts, tend to present early in life (2–4). Traditionally, the primary treatment of these lesions has been complete resection (5). However, sclerotherapy with doxycycline has been shown to a safe and effective minimally invasive treatment of macrocystic LMs outside of the abdomen (6), and is now the primary method of treatment in our institution. There have been previous isolated reports of sclerotherapy of abdominal LMs, with or without adjunctive resection, with variable results (7–9). Technical difficulties, potential complications from peritoneal spillage, and absence of proven preprocedural diagnosis have been cited as some of the reasons for resistance to the use of sclerotherapy in the treatment of abdominal LMs (5). Here we present 10 patients with intraabdominal LMs treated only with image-guided percutaneous doxycycline sclerotherapy. The purpose of this study was to evaluate the safety and efficacy of this treatment.
of abdominal, mesenteric, or retroperitoneal LM. Only patients who underwent sclerotherapy with doxycycline as the primary and sole method of treatment were included. This yielded a final study sample of 10 patients.

The clinical records and pre- and postprocedural imaging were then reviewed. Response to sclerotherapy was classified as complete if greater than 90% of the lesion had resolved based on imaging criteria and partial if the lesion had decreased in size by 25%–90%. Clinical response was assessed by history and physical examination on follow-up.

Technique of Sclerotherapy and Follow-up

Preprocedural cross-sectional imaging (computed tomography [CT] or magnetic resonance [MR] imaging) was reviewed in all patients before sclerotherapy. A single preprocedural dose of antibiotic agent (cefazolin 25 mg/kg) was administered intravenously. The malformation was accessed under sonographic guidance with needles of various sizes, from 21-gauge Chiba needles (Cook, Bloomington, Indiana) to 4-F Yueh Centesis Catheters (Cook; Fig 1). In two of the patients with smaller macrocysts, doxycycline was injected through the access needles. In the remainder, the needle was exchanged for Dawson–Mueller (Cook) or Total Abscession (AngioDynamics, Latham, New York) locking-loop drainage catheters. The catheters varied in size from 6 F to 10 F. In one patient a 14-F catheter was placed due to the presence of multiple hemorrhagic cysts. The location of the needle and catheter was confirmed with injection of diluted water-soluble contrast medium (Optiray-240; Mallincrodt, Hazelwood, Missouri). The fluid contents of the macrocysts were aspirated, and doxycycline was then infused under fluoroscopic guidance (Fig 2).

The doxycycline mixture was prepared by reconstituting 100 mg of doxycycline powder (Doxy 100; American Pharmaceutical Partners, Los Angeles, California) with 5 mL of saline solution and 5 mL of Optiray-240 to give a final concentration of 10 mg/mL. The volume of sclerosing agent infused was determined by the size of the lesion (typically one third to two thirds of the original volume).

If the malformation was small (< 50 cm³), the sclerosing agent was not drained. Care was taken not to overly distend the lesions in these cases to minimize risk of leakage at the puncture site. In the remainder of cases, after infusion of the sclerosing agent, the catheter was clamped for 4 hours and the lesion was then drained. Sclerotherapy was repeated through these drains on the next 1 or 2 days, depending on the size of the lesion. After the final sessions, the catheter was clamped for 4 hours and then drained and removed.

RESULTS

Patient characteristics and treatment results are outlined in the Table. Patients presented with chronic intermittent abdominal pain (n = 3), acute abdominal pain (n = 3); with associated fever and chills [n = 1] or decreasing hematocrit level n = 1]), abdominal distension with a palpable abdominal mass (n = 2), or on an incidental basis (n = 1). None of these patients had any previous treatment for the LM.

A preprocedural ultrasound (US) scan and cross-sectional imaging was performed in all patients (CT in six, MR imaging in four; Figs 2, 3). All LMs were noted to be thin-walled and multiloculated, with multiple intervening septations that exhibited some enhancement after the administration of contrast medium.

Given the location of the malformations and the severe discomfort associated with doxycycline injection (1), all procedures were performed under general anesthesia. In all cases, intravenous narcotic analgesic agent and nonsteroidal antiinflammatory analgesic agents (ie, ketorolac) were administered intra- and postoperatively. A single procedure was performed in two cases. In the remainder, sclerotherapy was repeated through the existing drains on the next day (n = 2) or the next 2 days (n = 6). The mean dose of doxycycline injected per session was 608 mg (range, 80–1,000 mg). The mean total dose of doxycycline injected per patient in multiple sessions was 1,230 mg (range, 80–3,000 mg).

During the second session of sclerotherapy in one patient, a small leak into the retroperitoneal space was identified. The injection was terminated on identification of the leak. The patient remained asymptomatic immediately postprocedure and at a 2-year follow-up, and complete resolution of the malformation was seen on follow-up imaging. No other immediate or medium-term complications during the follow-up period were identified.
After discharge, follow-up was performed by telephone at 1 day, 1 week, and 1 month. Patients then returned for evaluation 6–8 weeks after the procedure. At the time of the visit, the clinical symptoms had resolved in all 10 patients. Sonography was also performed at the visit, and demonstrated residual malformation in two patients. Of these two cases, one resolved after one further session of sclerotherapy. In the other child, who had a large combined microcystic/macrocystic LM of the retroperitoneum, there was only partial resolution despite three further procedures. No other sclerotherapy or resection was performed in the remainder of cases.

In eight of the 10 patients, further imaging was performed at a mean period of 6.4 months after the procedure (range, 4–12 mo). The modality used was CT in three cases, US in three cases, and MR imaging in two cases. Imaging demonstrated complete resolution of the malformation in seven of eight cases (Figs 2, 3). The other two patients remained asymptomatic during the follow-up period, but no further imaging was obtained.

**DISCUSSION**

LMs are developmental anomalies of lymphatic channels that do not communicate with the remainder of the lymphatic or venous system. Sprouting lymphatics may lose communication with the primitive lymphatic sacs or develop in an abnormal location (10). LMs have traditionally been divided into three main categories: macrocystic, microcystic, and combined. However, there remains considerable variability in the criteria used to designate a malformation as micro- or macrocystic (11,12). At our institution, only lesions or parts of lesions containing cysts that are too small to be accessed and aspirated with a hypodermic needle are designated as microcystic. The remainder of the LMs are classified as macrocystic. These criteria are based on the very different treatment options available for these malformations. The often-used size criteria of classifying microcysts as 1 cm or 2 cm in maximum diameter are arbitrary and not particularly useful, as thin-walled cysts of smaller diameter can be accessed and effectively sclerosed by using imaging guidance. In contrast, there is a much less favorable response to traditional sclerotherapy of microcystic malformations (13), even though there are some encouraging reports with the use of intralesional bleomycin (14,15).
The vast majority of the rare abdominal LMs are macrocystic in nature. The mesentery, with its rich lymphatic network, is the most common site of origin (4), with the omentum and retroperitoneum less commonly involved (16). Some previous studies have suggested that retroperitoneal involvement may be more common in adults (3), but this may be a reflection of the fact that retroperitoneal LMs are less likely to be symptomatic and therefore present at an early age. Overall, the majority of abdominal LMs are identified in childhood, and are symptomatic in as many as 88% (17). Children also tend to present more acutely, with shorter duration of symptoms (2,3,5). In contrast, symptoms in adults often tend to be mild and evolve over a period of months to years (3). Presenting signs and symptoms include abdominal pain, abdominal distension, nausea, vomiting, constipation, and diarrhea (2,4,18). In the present series, nine of 10 patients were symptomatic; three of them, all younger than 18 years of age, presented with acute abdominal pain. It has also been suggested that earlier detection in children may be related to smaller body habitus (5), as mesenteric LMs are palpable in one third of cases (19). In fact, three of the children in the present study had no pain, but presented after palpation of an abdominal mass on examination. Both male and female predominance have been reported in abdominal LMs (2,5), but the sample sizes reported were too small to confirm such a trend.

Over the years, there have been multiple case reports and small series describing the imaging findings in abdominal LMs (2–5,16,18–20). Sonographically, LMs are characterized as multiloculated thin-walled cystic structures, with multiple thin internal septations (4,21). The cysts are either anechoic or contain echogenic debris, reflecting the serous, hemorrhagic, or chylous contents. CT similarly demonstrates a unilocular or multiloculated cystic mass with thin walls that is predominantly of fluid attenuation, but may have areas of increased density reflecting hemorrhage (2,4). Isolated reports of MR imaging findings in abdominal LMs have highlighted a lesion that is hyperintense on fluid-weighted sequences with serosanguineous contents. MR imaging in all four of our patients who underwent it demonstrated a T2-hyperintense lesion with imperceptible walls and multiple thin, mild enhancing septations.

The current practice for imaging abdominal LMs relies primarily on US for initial diagnosis and postoperative follow-up. In view of the risks of radiation with CT and sedation with MR imaging, cross-sectional imaging is reserved for lesions that cannot be completely imaged or characterized with US.

Treatment of abdominal LMs is recommended because the incidence of complications such as bleeding, infection, bowel obstruction, and volvulus increases with time (2,22). Traditionally, complete resection of the abdominal LM has been advocated as the treatment of choice (3,5,18). However, complete resection frequently entails segmental bowel resection, which may be extensive in some cases (2,23). The recurrence rate after excision has been reported as 9.5% (23), which increases to 100% if the resection is incomplete (22).

Sclerotherapy with a variety of sclerosing agents, including ethanol, sodium tetradecyl sulfate, bleomycin, doxycycline, and OK-432 (picibanil), has been demonstrated to be effective in the treatment of macrocystic LMs (6,13,14,24). As in the present series, the mean age at presentation in previous studies was late childhood or early adolescence (6,13,14,24,25). In the majority of published cases, the treated malformation was located in the head and neck region (6,13,14,24,25), but successful sclerotherapy of abdominal LMs with a combination of sodium tetradecyl sulfate and alcohol (12) or doxycycline (6,9) has previously been reported. The authors prefer the use of doxycycline in view of its proven efficacy, availability, and good safety profile (6).

Doxycycline is a broad-spectrum antibiotic agent of the tetracycline family. Its exact mechanism of action remains unclear, although, in animal pleurodesis models, it has been shown to induce a cellular reaction with deposition of fibrin and collagen (26). Originally reported as an effective sclerosing agent of LMs in 1995 (9), it has proven to be an extremely reliable and safe sclerosing agent (6,25). In our
institution, sclerotherapy with doxycycline is now the treatment of choice in macrocystic LMs.

A minor complication rate of 10% was reported by Burrows et al (6) with the use of doxycycline for sclerotherapy, and complications included prolonged swelling, pain, and skin blisters. The complications were more common with microcystic or combined lesions and a higher doxycycline concentration (6). Major complications, particularly nerve damage, have also been reported, but are rare (6,27). In animal models, although perineural injection of doxycycline around an intact nerve is not neurotoxic, direct intraneural injection can result in significant decrease in neural function (27). In the present series, we had no clinically significant complications related to the sclerotherapy procedures.

Limitations of the present study include the small sample size and the retrospective design. In addition, although resolution of the malformations was confirmed with post-procedural cross-sectional imaging, no further periodic follow-up imaging was performed.

In conclusion, the medium-term results indicate that percutaneous image-guided sclerotherapy of abdominal LMs with doxycycline is safe and effective. Given the excellent response, doxycycline sclerotherapy may be considered as primary treatment for these malformations.

REFERENCES