

# **Octreotide in intestinal lymphangiectasia: Lack of a clinical response and failure to alter lymphatic function in a guinea pig model**

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Intestinal lymphangiectasia, which can be classified as primary or secondary, is an unusual cause of protein-losing enteropathy. The main clinical features include edema, fat malabsorption, lymphopenia and hypoalbuminemia. Clinical management generally includes a low-fat diet and supplementation with medium chain triglycerides. A small number of recent reports advocate the use of octreotide in intestinal lymphangiectasia. It is unclear why octreotide was used in these studies; although octreotide can alter splanchnic blood flow and intestinal motility, its actions on lymphatic function has never been investigated. A case of a patient with intestinal lymphangiectasia who required a shunt procedure after failing medium chain triglycerides and octreotide therapy is presented. During the management of this case, all existing literature on intestinal lymphangiectasia and all the known actions of octreotide were reviewed. Because some of the case reports suggested that octreotide may improve the clinical course of intestinal lymphangiectasia by altering lymphatic function, a series of experiments were undertaken to assess this. In an established guinea pig model, the role of octreotide in lymphatic function was examined. In this model system, the mesenteric lymphatic vessels responded to 5-hydroxytryptamine with a decrease in constriction frequency, while histamine administration markedly increased lymphatic constriction frequency. Octreotide failed to produce any change in lymphatic function when a wide range of concentrations were applied to the mesenteric lymphatic vessel preparation.

In conclusion, in this case, octreotide failed to induce a clinical response and laboratory studies showed that octreotide did not alter lymphatic function. Thus, the mechanisms by which octreotide induced clinical responses in the cases reported elsewhere in the literature remain unclear, but the present study suggests that it does not appear to act via increasing lymphatic pumping.

**Key Words:** *Intestine; Lymphangiectasia; Octreotide; Protein-losing enteropathy*

**I**ntestinal lymphangiectasia is a disease in which the bowel undergoes impaired lymphatic drainage, resulting in dilation of the lymphatic vessels and protein-losing enteropathy. The patient often presents with hypoproteinemia, hypoalbuminemia, lymphopenia and edema. The condition is divided into primary and secondary forms, with the former being recognized

## **L'octréotide contre la lymphangiectasie intestinale : Absence de réponse clinique et non-modification de la fonction lymphatique dans un modèle de cobaye**

La lymphangiectasie intestinale, qui peut être primaire ou secondaire, est une cause inhabituelle d'entéropathie par perte protéique. Ses principales caractéristiques sont l'œdème, la malabsorption des matières grasses, la lymphopénie et l'hypoalbuminémie. D'ordinaire, la prise en charge clinique inclut un régime faible en gras et des suppléments de triglycérides à chaîne moyenne. Quelques comptes rendus récents préconisent l'utilisation de l'octréotide contre la lymphangiectasie intestinale. On ne sait pas pourquoi l'octréotide a été privilégié dans ces études. Même s'il peut altérer le débit sanguin splanchnique et la motilité intestinale, ses effets sur la fonction lymphatique n'ont jamais été étudiés. Le cas d'un patient atteint de lymphangiectasie intestinale qui a dû subir un shunt après l'échec d'un traitement aux triglycérides à chaîne moyenne et à l'octréotide est présenté. Pendant la prise en charge de ce cas, toute la documentation scientifique existante sur la lymphangiectasie intestinale et tous les effets connus de l'octréotide ont été passés en revue. Puisque certains rapports de cas laissaient supposer que l'octréotide pouvait améliorer l'évolution clinique de la lymphangiectasie en altérant la fonction lymphatique, une série d'expériences ont été entreprises pour évaluer cette affirmation. Dans un modèle de cobaye établi, le rôle de l'octréotide dans la fonction lymphatique a été examiné. Dans ce système modèle, les vaisseaux lymphatiques mésentériques ont réagi au 5-hydroxytryptamine par une diminution de la fréquence de constriction, tandis que l'administration d'histamine entraînait une augmentation marquée de la fréquence de constriction lymphatique. L'octréotide n'a pu produire de modification à la fonction lymphatique lorsqu'une vaste série de concentrations ont été appliquées à la préparation des vaisseaux lymphatiques mésentériques.

Pour terminer, dans ce cas, l'octréotide n'a pu induire de réponse clinique, et les études de laboratoire ont révélé qu'il ne modifiait pas la fonction lymphatique. Ainsi, les mécanismes selon lesquels l'octréotide induisait des réponses cliniques dans les cas déclarés ailleurs dans la documentation scientifique demeurent incertains, mais la présente étude indique qu'ils ne semblent pas agir par une augmentation du pompage lymphatique.

as congenital in nature and linked to other diseases including Noonan's syndrome and Milroy's disease (1). Secondary causes of intestinal lymphangiectasia are often due to an underlying neoplasm or have an associated inflammatory component such as that in pericarditis, chemotherapeutic agent exposure and enteric infections (2,3).

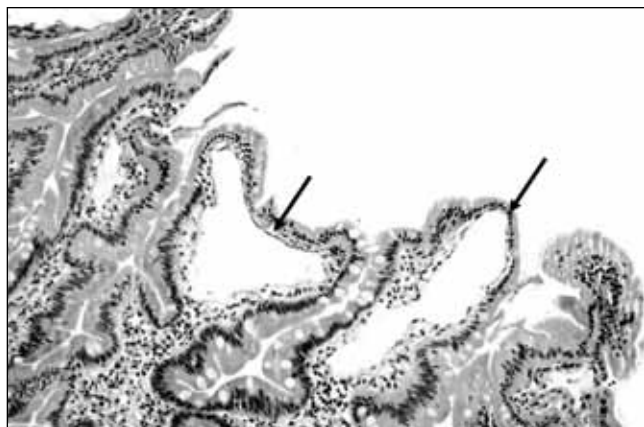
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**Figure 1)** Histological features of intestinal lymphangiectasia. Duodenal biopsy from the case presented showing markedly dilated lymphatic channels within the villi (arrows)

Medium chain triglyceride (MCT) supplementation, a low-fat diet and total parenteral nutrition have been the main components of the medical management of intestinal lymphangiectasia. Unfortunately, this therapy is often ineffective, is generally not well tolerated and is not without significant complications. Previous medical approaches such as antiplasmin therapy have produced mixed results and have generally been abandoned (4,5). Recently, the somatostatin analogue octreotide has been used in the treatment of intestinal lymphangiectasia. There are at least six case reports in the literature indicating that octreotide may be an effective treatment for this disease state (6-11). However, the mechanism by which octreotide improves the clinical features and associated laboratory values have yet to be identified. We present a patient with primary intestinal lymphangiectasia that failed to respond to both MCT and octreotide therapy. Ultimately, she underwent a shunt procedure which effectively improved her symptoms. To explore the mechanism by which octreotide may have improved lymphangiectasia in the cases reported in the literature, we conducted experiments using a guinea pig-derived mesenteric lymphatic preparation.

Intrinsic, rhythmic constrictions of the collecting lymphatic vessels are the primary mechanism by which lymph is propelled centrally. This rhythmic pumping of the collecting lymphatic chambers is essential for normal propulsion of intestinal lymph (12). This contractile activity persists after denervation and in the absence of endothelium (13). Although lymphatic pumping is a mechanism intrinsic to the smooth muscle present in the vessel wall, it can be altered by a wide variety of agents and drugs (14).

Octreotide and other somatostatin analogues inhibit growth hormone and suppress the secretion of serotonin and many other gastrointestinal peptides. These agents are extensively used in the management of variceal bleeding because they decrease splanchnic blood flow and, thus, portal venous pressure. Somatostatin immunoreactivity has been reported in submucosal plexus neurons associated with the lymphatic vessels of guinea pig ileum (15,16); of the multiple subtypes of somatostatin receptors, types two and five are the most common in the gastrointestinal tract (17). Thus, this suggests that somatostatin (and analogues) could affect lymphatic function. To investigate whether octreotide alters lymphatic pumping function, we applied varying doses of octreotide to lymphatic

vessels of the ileal portion of the guinea pig mesentery. This preparation is a well established model used to characterize both physiological and pharmacological properties of lymphatic pumping (14,18). Lymphatic vessels in this preparation range from 100  $\mu$ m to 300  $\mu$ m in diameter. The vessels are segmented into chambers (length 150  $\mu$ m to 500  $\mu$ m) by unidirectional valves. These vessels undergo rhythmic constrictions of five to 20 constrictions/min when luminal perfusion is applied (19-21).

The goal of the present paper is to review a clinical case of primary intestinal lymphangiectasia and investigate the mechanisms by which octreotide could act to modify the course of this often difficult to manage clinical entity.

## CASE PRESENTATION

A 21-year-old woman presented to the gastroenterology outpatient clinic with a history of primary lymphangiectasia. She initially presented to a pediatric gastroenterologist at the age of 13 years with an inability to gain weight and unexplained diarrhea. At initial presentation, she had chylous ascites, a chylous thorax and a serum albumin of 18 g/L (normal 35 g/L to 50 g/L). A lymphangiogram identified changes typical of lymphangiectasia. Additional investigations failed to show evidence of a lymphoma. A small bowel follow-through was normal and an abdominal computed tomography scan revealed marked ascites without other abnormalities or mass lesions. Small bowel biopsies revealed uniformly dilated lymphatic channels within the villi, diagnostic of intestinal lymphangiectasia (Figure 1). Initial treatment included MCT supplementation, a low-fat diet and weekly therapeutic paracenteses of up to 20 L thick chylous fluid.

At 16 years of age, a saphenoperitoneal shunt was performed but was unsuccessful due to repetitive occlusions. Based on the case reports in the literature, at 22 years of age, she was started on a course of octreotide (400  $\mu$ g/day subcutaneously for one year) (6-9,22). During the octreotide trial, she was maintained on the same low-fat diet and supplemental MCT. Throughout the course of octreotide therapy, the serum albumin did not change and ranged between 14 g/L and 19 g/L (normal 35 g/L to 50 g/L). The frequency and volume of therapeutic abdominal paracenteses also did not change. After six months of therapy, when it was clear that no effect was being observed, the pancreatic lipase inhibitor orlistat was added, but a further six months of co-therapy did not result in any appreciable change in objective markers of disease activity. At the end of over a year of therapy, a LeVeen shunt was placed but it occluded within a few days. A radiologically inserted subcutaneous shunt between the abdomen and right subclavian vein was then placed and functioned well with complete resolution of the need for therapeutic paracentesis; her albumin returned to within normal limits.

During her course of therapy, the authors reviewed all of the existing literature on octreotide and lymphatic function. In some of the case reports that showed that octreotide resulted in significant clinical improvements, it was suggested that octreotide may be acting by altering lymphatic function. Clearly, octreotide has been shown to alter splanchnic blood flow, which theoretically could alter hydrostatic pressure and lymph flow (23). However, direct studies on the role of octreotide on lymphatic function have not been reported. Thus, a series of experiments were undertaken to assess the role of octreotide on lymphatic function.

## METHODS

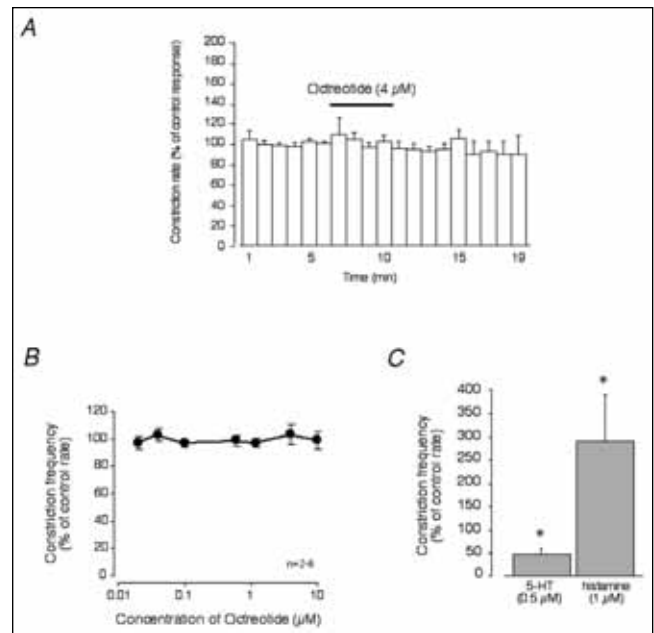
A well established guinea pig model system was used to assess lymphatic pumping (14,18,19). Guinea pigs (seven to 15 days of age) of either sex were killed by decapitation during halothane anesthesia. Collecting lymphatic vessels (diameter less than 230  $\mu\text{m}$ ) supplying the ileum were dissected together with the associated artery and vein, and were left intact within the surrounding mesentery. The tissue was then bathed in a physiological saline solution and the pH was maintained at 7.4 by constant bubbling with 95%  $\text{O}_2$ :5%  $\text{CO}_2$ . The mesentery was used to pin out the tissues on the Sylgard-coated base of a 2 mL organ bath, mounted onto the stage of an inverted microscope (Olympus CK40, Carsen Group Inc, Canada), and lymphatic vessels were continuously superfused at a flow rate of 3 mL/min with the physiological saline solution heated to 36°C. To induce a consistent rate of vessel constrictions, the vessel lumen was perfused through a fine glass cannula inserted into the vessel. The cannula was connected to an infusion pump (KD Scientific, USA) via Teflon tubing and the vessel was perfused in the direction of the valves at a flow rate of 2.5  $\mu\text{L}/\text{min}$ . A low-calcium solution (0.3 mM calcium chloride) was used to avoid blocking of the cannula (19). Contractile activity of lymphatic vessel chambers was monitored using a video camera attached to the microscope, with output recorded on videotape and change in vessel diameter analyzed in real time or offline using a video dimension analyzer (Living System Instrumentation, USA) and recorded on a computer (iMac, Apple Inc, USA) via an analogue to digital converter (PowerLab/4SP, AD Instruments, USA).

A 5 min control period of contractile activity was recorded before octreotide (Sandostatin, Novartis, Switzerland) was applied. Varying concentrations of octreotide (20 nM to 10  $\mu\text{M}$ ) were applied to the preparation for 4 min periods via the superfusion solution. A washout period of at least 30 min was allowed between successive applications. Contractile activity (contraction/min) recorded during the 4 min of treatment were averaged (mean  $\pm$  1 SEM) and expressed as a percentage of the mean of the preceding 5 min control period, as described previously (20,21). Lymphatic vessels respond to 5-hydroxytryptamine (5-HT, Research Biochemical Inc, USA) with a decrease in constriction frequency while histamine (ICN Biochemicals, USA) increases the frequency of lymphatic vessel constriction (20,21). Therefore, 5-HT and histamine were used to assess the responsiveness of the vessels studied and were applied successively to the preparation for 1 min followed by the above washout period.

These procedures were approved by the University of Calgary Animal Care and Ethics Committee.

## RESULTS

Under intraluminal perfusion (2.5  $\mu\text{L}/\text{min}$ ) with a physiological saline solution, mesenteric lymphatic vessels spontaneously and rhythmically constricted at a frequency between nine and 26 constrictions/min. In preparations from the six animals tested, octreotide (4  $\mu\text{M}$ ) applied into the superfusion solution during 4 min periods did not affect either the constriction frequency or lymphatic vessel pumping activity (Figure 2A). Figure 2B shows the absence of an effect of octreotide over a wide concentration range (20 nM to 10  $\mu\text{M}$ ). Despite the absence of response to octreotide, these vessels responded to treatment with 0.5  $\mu\text{M}$  5-HT with a decrease in constriction frequency (47 $\pm$ 11% of control) and to the application of 1  $\mu\text{M}$  histamine with an increase in pumping (288 $\pm$ 101% of control) as previously described (20,21).



**Figure 2** Effect of octreotide on the contractile activity of guinea pig mesenteric lymphatic vessels. **(A)** Time course histogram showing the mean response ( $\pm$  SEM) of five vessels to 4  $\mu\text{M}$  octreotide applied for 4 min (horizontal bar). **(B)** Concentration-response relationship of the effect of octreotide. **(C)** Histograms of the effects of 5-hydroxytryptamine (5-HT) and histamine on the contractile activity in the same vessels investigated in **A** and **B**. \* $P<0.05$ , paired Student's  $t$  test

In summary, although pumping of guinea pig mesenteric lymphatic vessels could be altered by known modulatory agents, it was not affected by octreotide over a wide range of concentrations.

## DISCUSSION

This is the first published report, that we are aware of, in which octreotide therapy failed to improve clinical parameters in a patient with primary intestinal lymphangiectasia. Furthermore, our laboratory studies failed to show that octreotide altered lymphatic function as assessed by monitoring contractile frequency.

Some of the factors that could have affected our results are that animals were anesthetized before sacrifice, and that the isolation of the lymphatic vessels clearly could have altered lymphatic responsiveness. Although the associated artery and vein were left intact within the surrounding mesentery, clearly there could have been artifact introduced. This is, however, a well described lymphatic preparation and, as previously mentioned, it responded well to other agents known to modulate lymphatic contractility (14,19). Octreotide has numerous actions both within the gastrointestinal tract and systemically; thus, this isolated preparation did not assess the possibility that octreotide could alter lymphatic function indirectly.

There have been at least six published case reports indicating the efficacy of octreotide in patients with intestinal lymphangiectasia (6-11). The first case of successful octreotide treatment was described by Bac et al (8) in 1995, in a patient with secondary intestinal lymphangiectasia that was also treated with corticosteroids. Ballinger and Farthing (7) described the successful



use of octreotide in a patient with primary intestinal lymphangiectasia and showed that octreotide decreased enteric protein loss, and led to resolution of pleural effusions and improvement in serum albumin levels. Kuroiwa et al (6), Strehl et al (11) and Klingenberg et al (9) reported individual patients with primary intestinal lymphangiectasia who also were successfully treated with octreotide; remarkably, one study (6) noted resolution of both endoscopic and histological changes. Recently, Lee et al (10) reported that octreotide improved protein-losing enteropathy due to secondary lymphangiectasia thought to be induced by hepatitis B-associated liver cirrhosis.

Thus, the current literature reports that octreotide has improved the clinical and laboratory features of intestinal lymphangiectasia in six different patients: four with primary intestinal lymphangiectasia and two with secondary intestinal lymphangiectasia. We could not identify any cases in which a patient with intestinal lymphangiectasia failed to respond to octreotide. Anecdotally, we and some of our other colleagues have found that not all patients respond to octreotide. Thus, we feel this 100% success rate likely represents a publication bias towards 'positive studies'.

Although the above case reports indicate a benefit with the use of octreotide, the mechanism of action has not yet been identified. One speculation is that octreotide reduces intestinal blood flow, decreasing triglyceride absorption and resulting in decreased lymphatic flow and obstruction. Cohen et al (24) found that, in patients receiving octreotide for acromegaly, octreotide dramatically reduced growth hormone, insulin and insulin-like growth factor levels, and produced a marked reduction in serum triglycerides and total cholesterol. One of the mechanisms by which octreotide appears to decrease serum triglycerides is by preventing absorption from the intestinal lumen; octreotide therapy increased fecal fat excretion in patients with acromegaly and healthy volunteers (25-27). How octreotide decreases fat absorption remains unclear but, clearly, octreotide can decrease pancreatic exocrine secretion and alter bile secretion, both of which can alter absorption (28). Octreotide can also dramatically alter gastric emptying and intestinal transit, but it is unclear if these changes affect lipid absorption (27,29).

Octreotide can inhibit the secretion of many mediators of intestinal and pancreatic function but, specifically, it can potentially inhibit release and action of serotonin (5-HT) (30,31). This may represent one of the mechanisms of action by which octreotide induced clinical improvement in the above case reports; our studies and studies by other investigators clearly show that 5-HT can markedly reduce lymphatic pumping, leading to dilated vessels and lymph stasis (21,32).

Wiest et al (33) studied octreotide on the vasoconstrictive responses of the superior mesenteric vein in a rat model of portal hypertension. Octreotide did not affect baseline perfusion pressures but alpha-1-adrenergic and endothelin-1-mediated vasoconstriction were potentiated by octreotide. This response was enhanced by nitric oxide inhibition and suppressed by inhibition of protein kinase C, phospholipase A<sub>2</sub> and cyclooxygenase (33). Similar such studies have yet to be reported in lymphatic vessels. Clearly, these studies cannot be directly compared with lymphatic function but they do show that octreotide can modulate smooth muscle contraction.

One of the dynamic features of the lymphatic system is that lymphatic flow can alter lymphatic pumping. Several studies have shown that imposed flow can inhibit the active lymph pump in both mesenteric lymphatics and in the thoracic duct

(23,34). The active pump of the thoracic duct appears to be more sensitive to flow than the active pump of the mesenteric lymphatics (34). Gashev et al (34) reported that imposed flow reduced the frequency and amplitude of the contractions and, accordingly, the active pump flow. In this setting, nitric oxide (NO) was partly but not completely responsible for the influence of flow on the mesenteric lymph pump. Exposure to NO mimicked the effects of flow whereas inhibition of NO synthase attenuated but did not completely abolish the effects of flow (34). In our study, we did not directly assess octreotide in flow-related lymphatic pumping because flow was maintained constant.

At present, there are limited options in the treatment of intestinal lymphangiectasia. MCT supplementation and a low-fat diet are the recommended first line interventions, and the only other therapy that has shown some signs of clinical success is octreotide. It is unclear why our patient failed to respond to octreotide. It is possible that octreotide may be effective in mild to moderate disease but may not be effective in more severe cases. Our patient also failed to respond to a lipase inhibitor. Such therapy has not been previously reported in the literature but, due to her significant symptoms and requirement for massive frequent paracentesis, we felt that attempts at inhibiting lipid absorption would be beneficial. From our experience, it appears that those that have severe intestinal lymphangiectasia who fail to respond to octreotide may ultimately require a shunt procedure.

In summary, the mechanism of action of octreotide in intestinal lymphangiectasia remains unclear but the present studies suggest that it does not appear to act via a direct effect on lymphatic pumping. Further studies are required to determine if octreotide may be altering lymphatic flow, or if it functions indirectly via its numerous actions on vascular tissues or possibly by altering the regulation of gastrointestinal hormones and other mediators.

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