

# Sclerosing mesenteritis: a comprehensive clinical review

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**Abstract:** Sclerosing mesenteritis is a rare disease entity initially described in 1924 with a prevalence reported to be less than 1%. Sclerosing mesenteritis is a comprehensive term used to describe three almost similar clinical entities including mesenteric panniculitis, retractile mesenteritis, and mesenteric lipodystrophy which only differ by their histology. The etiology of sclerosing mesenteritis is uncertain, but the disease has been associated with trauma, autoimmune disease, surgery, and malignancy. The typical presenting symptom is the abdominal pain, but sclerosing mesenteritis has a broad constellation of presenting symptoms which often makes consideration of the diagnosis unlikely. Treatment for this little-understood disease ranges from surgical intervention for patients presenting with obstructive symptoms to immunosuppressive medical therapy for patients presenting with pain. The purpose of this article is to provide an overview of the literature relevant to the diagnosis, etiology, and management of this condition in hopes of making physicians aware of this unique condition.

**Keywords:** Sclerosing mesenteritis; mesenteric lipodystrophy; retractile mesenteritis; mesenteric panniculitis

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## Introduction

Sclerosing mesenteritis is a relatively uncommon condition with an estimated prevalence <1% and is characterized by chronic nonspecific fat necrosis and inflammation/fibrosis of the abdominal mesentery (1). Chronic uncontrolled inflammation and fibrosis leads to a myriad of gastrointestinal complaints including but not limited to abdominal pain, nausea/vomiting, weight loss, and fever. This review article serves to provide an overview of the published literature to increase awareness for the medical providers caring for and evaluating patients with gastrointestinal disease (2,3).

## History/terminology

Sclerosing mesenteritis was first recognized as a clinical

entity by Jura in 1924 and was termed as “retractile mesenteritis” (4). It was again described later in 1947 and 1955 by two different physician groups (5,6). Initially, it was thought that the described entity was a part of early Whipple disease (6) which showed the presence of lipid-laden macrophages (lipodystrophy) on pathological examination. It was more clearly delineated by Ogden *et al.* in 1960 (7), where they presented a case series of seven patients describing the constellation of symptoms and findings. They called it “mesenteric panniculitis” because of its histologic similarity to Weber-Christian disease. Since then, we have come to learn more about this entity and the term sclerosing mesenteritis is now broadly given to a group of three similar clinical entities including mesenteric panniculitis, retractile mesenteritis, and mesenteric lipodystrophy: in large part due to the work of Kipfer (8).

## Terminology

Because of its variable pathological findings, sclerosing mesenteritis has been called numerous other names such as mesenteric lipodystrophy, mesenteric panniculitis, Weber-Christian disease (9), liposclerotic mesenteritis (10), and mesenteric fibrosis (2,11). Patients with a greater degree of inflammation and fatty necrosis have been described as having sclerosing panniculitis (2), and patients with active adipocyte necrosis are said to have mesenteric lipodystrophy. Patients with increased presence of fibrosis are termed to have “retractile mesenteritis”.

It has been thought that sclerosing mesenteritis is representative of three different and distinct entities including retractile mesenteritis, mesenteric panniculitis, and mesenteric lipodystrophy (12-14). The variation on naming is reflective of the different pathologic findings on the biopsy. Although it is possible to separate these three findings by histology, there is a debate as to whether this is reflective of one disease process with progression or completely separate entities (15). To date, there has only been one description of sclerosing mesenteritis as a progressive disease process. The patient's often have one predominant histologic feature (16). Given that there has been little evidence presented of histologic progression from lipodystrophy to fibrosis it seems likely that each entity is its own separate diagnosis but contained within a spectrum of the disease of sclerosing mesenteritis (2,17).

## Epidemiology

Although described as a rare disease, it is thought that the incidence of sclerosing mesenteritis could be as high as 3.4%, with a reported range of 0.16–3.4% (1,18,19). This incidence is difficult to determine as many patients diagnosed initially with primary sclerosing mesenteritis are found to have secondary sclerosing mesenteritis usually due to underlying malignancy. The reported incidence also varies by the method of determination, such as if diagnosed by the histology versus radiologic criteria. A study conducted by Kuhrmeier utilizing patients' autopsy as a diagnostic criterion suggested an incidence of approximately 1% based on the findings of sclerosing panniculitis in nine of the 712 autopsies (18). Multiple studies have also used imaging criteria for the diagnosis of sclerosing mesenteritis. In a prospective evaluation of 7,000 consecutive abdominal computed tomography (CT) scans, Daskalogiannak

reported an incidence of about 0.6%. Several other studies have shown similar rates (1-3). However, the main limitation of these imaging-based studies is lack of biopsy for confirmation of diagnosis as well as lack of standard imaging criteria for diagnosis (20).

Sclerosing mesenteritis is commonly diagnosed in the fifth to seventh decade of life although a case report with a three-year-old patient has also been published (3,12). A recent systematic review of 192 cases of sclerosing mesenteritis showed an age range of 3–88 years with a mean age of 55  $\pm$  19.2 years (3). Most of the studies have been performed on the Caucasian population which limits generalization across the multiple ethnicities. Most studies show a consistent relative preponderance of male gender (3,21), however, this has been debated in some studies. Prospective studies by Daskalogiannak *et al.* (1) and Coulier *et al.* (19) showed a slightly higher female predominance. In a prospective study of 94 patients with mesenteric panniculitis (48 idiopathic) diagnosed with strict radiologic criteria, there was a definite male predominance (20).

## Etiology

The etiopathogenesis of sclerosing mesenteritis remains unclear till now. A better understanding of the pathogenesis may eventually allow for more formal diagnostic criteria and eventually better management. A clear understanding of the pathogenesis may also additionally allow for a more formal narrowing of the diagnosis. At least four different pathologic processes have been proposed as etiologies of development of sclerosing mesenteritis including abdominal surgery/trauma, autoimmune phenomenon, paraneoplastic process, and ischemia/infection.

Abdominal surgery has frequently been shown to be a precursor to the development of sclerosing mesenteritis. This iatrogenic etiology has been reported back to the original case series of sclerosing mesenteritis by Ogden and Jura (4,16). The proposed mechanism is possibly a genetically inherited abnormal response to wound healing (2). Several case series have reported the association of sclerosing mesenteritis with prior abdominal surgery ranging from as low as 24% to as high as 53% (3,15,22). A case series published by Kipfer *et al.* suggested that the introduction of foreign substances in the abdominal cavity can produce symptoms and findings similar to the sclerosing mesenteritis. However, there has never been any confirmed findings to support this hypothesis, but the use of powdered

surgical gloves has been implicated in the development of abdominal fibrosis (8,22).

Role of autoimmunity as an etiology of sclerosing mesenteritis has been purported by several authors. Multiple case reports have been published which showed the possible association of sclerosing mesenteritis to Riedel thyroiditis, retroperitoneal fibrosis, and primary sclerosing cholangitis (3). Although the clinical course of sclerosing mesenteritis is variable and often transitions into remission without treatment; a response to immunomodulatory medications would suggest an autoimmune process. Patients have been treated previously with glucocorticoids, azathioprine, tamoxifen, infliximab, intravenous immunoglobulins, and cyclophosphamide (3,23). Sclerosing mesenteritis has also been proposed to be IgG4 mediated sclerosing disorder because of abundant tissue infiltration by IgG4-positive plasma cells (22,24).

One of the single biggest debate pertaining to sclerosing mesenteritis has been the question of whether sclerosing mesenteritis is a paraneoplastic syndrome. This is one area of sclerosing mesenteritis where the most research and debate has persisted. This initial question was first raised by Ogden *et al.* in 1965 in a follow-up study of the original case series published in 1960 (7,16) where two out of seven patients developed lymphoma. This concern was again noted in a case series published in 1974 by Kipfer *et al.* in which 8/53 patients were found to have lymphoma and 16/53 had other malignant neoplasms (8). These concerns have continued to abound throughout the literature. Multiple other studies have demonstrated statistically concerning rates of associated malignancy with a diagnosis of sclerosing mesenteritis with a reported range from 8.9–56% (17,21,24–26). Gogebakan *et al.* showed no statistical difference in matched-pair analysis between sclerosing mesenteritis patients with underlying malignancy and controls with 50.6% and 60.2% respectively while van Putte-Katier showed 48.9% and 46.3% respectively which was statistically significant (21,24). Contradictory results of the above two studies fail to provide a clear association of sclerosing mesenteritis and malignancies.

Although infection has been proposed as one of the mechanisms of sclerosing mesenteritis development, there has been very little evidence provided in the published case series or large retrospective chart reviews. Multiple case reports have detailed the history of chronic infections including tuberculosis, histoplasmosis, Whipple's disease, typhoid fever, and syphilis that have possibly led to the development of sclerosing mesenteritis (27).

## Diagnosis

### *Symptoms/findings*

Symptoms of sclerosing mesenteritis are non-specific, and up to 15% of patients can even be completely asymptomatic when it is found on the imaging performed for some other reasons (1). The initial case series published in the early 1950s did include a large proportion of patients who were diagnosed with sclerosing mesenteritis because of abnormal physical examination findings suggestive of abdominal masses (7). An increasing number of patients are now being diagnosed incidentally on abdominal CT scans obtained for other reasons. The duration of symptoms varies considerably which can be as short as 24 hours or can be as long as ten years. However, the most common presenting complaint is abdominal pain. A recently published systematic review of 192 cases of sclerosing mesenteritis revealed the symptomatology as abdominal pain in 78.1%, fever 26.0%, weight loss 22.9%, diarrhea 19.3%, vomiting 18.2%, anorexia 13.5%, constipation 10.9%, bloating 9.4%, malaise 5.7%, nausea 5.7%, pain with eating 4.7%, and fatigue 2.1% of patients (3). A significant challenge with these symptoms is that all are associated with a myriad of other diseases. The non-specific complaints in addition to the infrequency of diagnosis make the clinical recognition very difficult especially without imaging studies.

### *Laboratory studies*

There is no specific laboratory biomarker/test available for the diagnosis of sclerosing mesenteritis although the elevation in inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) has been reported in as high as in 80% of cases (28).

### *Imaging characteristics*

Abdominal imaging is the mainstay for the diagnosis of the sclerosing mesenteritis, and the advent of CT scan has drastically improved the diagnostic incidence of sclerosing mesenteritis. Since 1924 when the sclerosing mesenteritis was first recognized and especially after 1980 the number of case reports and case series have dramatically increased (1,4).

Sclerosing mesenteritis can be visualized on abdominal ultrasound, CT scan, and MRI, but CT scan is the most utilized imaging modality recorded in the literature (29). However, in the initially published literature, barium radiographs of the abdomen were also utilized, but it was

useful only for severe cases where significant external compression of the bowel had already occurred distorting the underlying anatomy (16).

One of the specific CT scan signs to diagnosis sclerosing mesenteritis is a “fat ring sign” (1,15,28) but presence of “pseudo-capsule” also raise the suspicion of sclerosing mesenteritis (15). Infrequently, a sign of “misty mesentery” has also been described which is an increased in mesenteric attenuation with the presence of small nodes in the absence of a discrete soft-tissue mass suggestive of sclerosing mesenteritis (30). In the year 2011, Coulier published a five-sign CT imaging criteria specifically for mesenteric panniculitis. These criteria were later accepted by many authors and subsequently were used in many other studies for the diagnosis of sclerosing mesenteritis (19,21). These five diagnostic signs included the presence of a well-defined “mass effect” on neighboring structures (sign 1) constituted by mesenteric fat tissue of inhomogeneous higher attenuation than adjacent retroperitoneal or meso-colonic fat (sign 2) and containing small soft tissue nodes (sign 3). It may typically be surrounded by a hypo-attenuated fatty “halo sign” (sign 4) and an hyperattenuating pseudo-capsule may also surround the entity (sign 5). However, these diagnostic criteria were not histologically verified, but they have overall come to represent the closest general standards available (31).

### Pathology

Pathologic analysis of biopsy results for sclerosing mesenteritis has been well established. The clinical debate that has persisted pertains to whether sclerosing mesenteritis is representative of three different microscopic pathologic entities or just two.

Although no definitive gross pathologic criteria have been defined, Kipfer *et al.* proposed the sclerosing mesenteritis to have three gross pathological clinical categories. These categories have served as the defacto standard to understand the gross pathology of sclerosing mesenteritis.

- ❖ Type I: diffuse mesenteric thickening: the base of the mesentery was thickened up to 10 cm in width with dirty gray to yellow-orange fat appearance. The thickening typically ended within 3–5 cm of the mesenteric border.
- ❖ Type II: single discrete tumor: often located in the jejunal mesentery. The mass can be smooth or multi-lobular, firm or rubbery in consistency.
- ❖ Type III: multiple discrete tumors: tumors are

noted to have the same consistency and features as described in type II (8).

The primary microscopic histologic feature of the three clinical types of sclerosing mesenteritis is the same, but within each microscopic histology there has been a debate whether the sclerosing mesenteritis is two discrete types or three (2). Emory *et al.* reviewed 84 cases of sclerosing mesenteritis and provided the most consistently referenced histologic standard and definition. They divided sclerosing mesenteritis into three categories which are sclerosing (retractile) mesenteritis, mesenteric panniculitis, and mesenteric lipodystrophy depending on variable degrees of fibrosis, chronic inflammation, and fat necrosis. Histological specimens with more fibrosis are categorized as “retractile” disease, panniculitis has fat necrosis with an inflammatory component, and lipodystrophy specimen have predominately fat necrosis. Although, most authors admit that these components are simultaneously present within any histology specimen (2). There has been limited evidence to support that sclerosing mesenteritis is a progressive process moving from lipodystrophy to retractile mesenteritis.

### Differential diagnosis/mimics

CT findings that are similar to sclerosing mesenteritis include lymphoma, carcinoid tumor, carcinomatosis, primary mesenteric mesothelioma, and mesenteric edema (31). Moreover, any disease process that impacts the mesentery can produce CT imaging findings that mimic sclerosing mesenteritis. The challenge with the sclerosing mesenteritis is that due to its non-specific presenting symptoms the differential diagnosis very broad.

### Management

#### Surgical management

Given the broad differential and the similar imaging findings of several neoplastic processes, a significant number of patients usually undergo CT guided biopsy to establish the diagnosis. However, the significant challenge faced by surgeons and healthcare practitioners caring for these patients is whether an aggressive approach of surgical resection should be pursued. Given the self-limited nature of this condition; in a significant number of patients, it would seem prudent to avoid surgical intervention beyond diagnostic sampling. In some early

published case series, patients were predominantly treated with surgical resection but with moderate to fair results. In a combined retrospective and prospectively collected data of 92 patients followed for ~20 months, Akram *et al.* showed that 44 (48%) patients ultimately received some type of therapeutic treatment. Twenty four out of 44 patients (56%) received some form of pharmacotherapy, and with 20 out of 44 patients (45%) received surgical intervention. The most common indication for surgical intervention was the development of intractable bowel obstruction in these patients. In a significant number of these patient's, the mass itself was primarily unresectable, and they required bowel resection subsequently. However, patients who received surgery as the primary intervention, only 2 of 20 (10%) responded to surgery alone (22) and received pharmacotherapy mainly in the form of tamoxifen. This study alone, and as the only study with a prospective analysis showed minimal benefit from surgical intervention.

### Observation

Although the diagnosis of sclerosing mesenteritis can carry a considerably broad differential, with significant concern for malignancy, often patients have minimal to no symptoms at presentation. If histologic sampling of the tissue is consistent with sclerosing mesenteritis, it seems that patients may be managed with watchful waiting and monitoring for the development of symptoms that may require intervention. This is also in consensus with the algorithm proposed by Akram *et al.* (22).

### Medical therapy

A significant variety of medical interventions have been used and reported in the literature to treat this challenging diagnosis. Medical treatments have mainly focused on the use of steroids (3), and less frequently colchicine, tamoxifen, 6-mercaptopurine, antibiotics, azathioprine, methotrexate, infliximab have also been used (3). Some case reports about the use of cyclophosphamide, IVIG, D-penicillamine, thalidomide, and tacrolimus have also been published but the use of these agents is less common (32).

We would like to suggest that when evaluating the necessity of treatment, it is important to evaluate the nature of the symptoms experienced by patients. Patients who remain symptomatic and are not surgical candidates then medical therapy has been recommended by several authors (3,22). In one of the largest studies published to

date by Akram *et al.*, they proposed a medical treatment algorithm of using tamoxifen twice daily and a prednisone taper completed over three months. In their study tamoxifen with prednisone was utilized in 20 patients. Of these 12 of 20 responded to therapy within 12–16 weeks, with 6 of 20 having persistent symptoms and 2 of 20 showing progression. Of the other medical therapies studied there was no treatment success. A variety of case reports have shown success with other therapies but all of which have been isolated reports. As proposed by Akram *et al.* it seems reasonable to treat patients with their approach of tamoxifen and prednisone if they are not a surgical candidate and continue to have symptoms not explained by another etiology.

### Summary

Sclerosing mesenteritis has been well described throughout the literature, but even with its significant presence within the literature, our understanding is still very limited. Progression in the development of firm recommendations for management has been hindered by the variety of clinical terms utilized to describe the same clinical entity.

There has been no recognition of one unifying theme or etiology for sclerosing mesenteritis. It is best characterized as idiopathic at this time. In the future, we may better understand the disease if we can further categorize different presentations as specific for different etiologies. It has been suggested that there may be a primary and a secondary sclerosing mesenteritis. With the existing concern for sclerosing mesenteritis being a paraneoplastic syndrome it may be best to exclude cases associated with malignancies and treat them as secondary sclerosing mesenteritis. Additionally, further research should be conducted to better explore the possible link between IgG4-mediated disease and sclerosing mesenteritis.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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