Sclerosing Mesenteritis

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11.1 Introduction

Sclerosing mesenteritis (SM) is a rare, idiopathic disorder of unknown etiology that involves the adipose tissue of the mesentery, being characterized by chronic and nonspecific fibrous inflammation [13, 42]. A PubMed search at the time of writing (October 2015)[1] revealed 517 publications on the subject of SM, the majority being anecdotal case reports and small case series. This suggests that SM is still considered to be a rare or at least uncommon disease or that the disease is underrecognized in clinical practice [39, 41, 42]. Much can be learned from some large case series and prevalence studies published over the last four decades from single-center experience or from cumulative literature data [1, 10, 13, 15, 42, 59]. In this chapter, we provide an overview of this intriguing disease, including its potential pathogenesis, the possible association with other fibroinflammatory disorders, and outline the

[1] PubMed search strategy:
("panniculitis, peritoneal"[MeSH Terms] OR ("panniculitis"[All Fields] AND "peritoneal"[All Fields]) OR "peritoneal panniculitis"[All Fields] OR ("mesenteric"[All Fields] AND "panniculitis"[All Fields]) OR "mesenteric panniculitis"[All Fields]) OR ("panniculitis, peritoneal"[MeSH Terms] OR ("panniculitis"[All Fields] AND "peritoneal"[All Fields]) OR "peritoneal panniculitis"[All Fields] OR ("sclerosing"[All Fields] AND "mesenteritis"[All Fields]) OR "sclerosing mesenteritis"[All Fields]) OR ("panniculitis, peritoneal"[MeSH Terms] OR ("panniculitis"[All Fields] AND "peritoneal"[All Fields]) OR "peritoneal panniculitis"[All Fields] OR ("mesenteric"[All Fields] AND "lipodystrophy"[All Fields]) OR "mesenteric lipodystrophy"[All Fields])

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diagnostic and therapeutic approach, with emphasis on imaging and medical treatment.

11.2 Definition and Nosology

First described by Jura in 1924 as "retractile mesenteritis" [26], numerous other terms have been used to describe this disease depending on the predominant histology, including mesenteric lipodystrophy, sclerosing mesenteritis, mesenteric Weber-Christian disease and mesenteric fibrosis [13, 15, 30, 32, 42]. The variety of terms, used particularly in older literature, in part reflects the variable proportion of histologic changes from case to case (i.e., chronic inflammation, fat necrosis and fibrosis) and the absence of a unifying concept [15]. It is now increasingly accepted that these different terms or diagnostic entities represent a spectrum of a single disease characterized by nonspecific inflammation of the mesenteric fat that may ultimately lead to fibrosis and retraction, and that SM is probably the most appropriate encompassing term [13, 15, 24].

11.3 Epidemiology

SM is being recognized with increasing frequency at computed tomography (CT) imaging due to the increased use of abdominal diagnostic imaging and the identification of typical signs for SM on CT [59]. Data on the prevalence of SM are scarce with conflicting results. One study reported a prevalence of 0.6 % among patients who underwent CT scanning for various reasons [10], while others reported a much higher prevalence ranging from 3.4 to 7.8 % depending on the CT-criteria used [8]. Other studies reported a lower prevalence, ranging from 0.16 to 0.6 % among patients who underwent CT scanning [19, 53, 63]. However, these studies were all based on a keyword search instead of actually reanalyzing all CT scans for signs of SM, which may lead to underreporting. Reanalyzing all CT scans for signs of SM in 3,820 patients using very strict CT criteria and exclusion criteria, a prevalence of 2.5 % was found by van Putte et al. [59]). SM typically presents in patients between the 6th and 7th decades of life with a male predominance [13, 15, 59, 61]. However, it may occur in every age group and pediatric cases have been described [1, 13]. SM seems more common in Caucasian men [7, 59].

11.4 Etiopathogenesis

11.4.1 General Comments

The etiology of SM remains obscure. The disease may occur independently or in association with other disorders, suggesting that the pathogenic mechanism may be

a nonspecific response to various stimuli [13, 15, 42]. Various causal factors have been suggested, notably malignancy and abdominal trauma (including surgery) [1, 7, 44, 50]. Mesenteric ischemia may also play a role in the pathogenesis of SM [13, 15, 41, 42]. Anecdotally, SM has been associated with auto-immune disorders, certain infections, granulomatous disease and fibrosis at other sites [13, 15, 42]. Recent data suggest that SM may in some cases be a manifestation of immunoglobulin G4-related disease (IgG4-RD) [37, 49, 64]. Environmental factors may also be involved, smoking being linked to the development of SM [12]. Given the frequency of smoking in the population at large, this needs further investigation. Some authors suggest that a high prevalence of SM explains the spontaneous association with numerous and probably unrelated clinical situations/disorders found in the literature [7, 44, 50].

11.4.2 Malignancy

SM has a poorly understood association with underlying malignancy with conflicting results in the literature, which suggests that it may at least in some patients be a paraneoplastic phenomenon [10, 19, 53, 63]. Reported prevalence of malignancies, usually discovered before the onset/diagnosis of SM, is high and ranges from 23 to 49 % [19, 32, 59, 63]. Kipfer et al. suggested that SM may be a nonspecific response to an underlying abdominal malignancy [32]. As SM occurs typically in older and male patients, it inevitably increases the likelihood of cancer development in general and more specific prostatic cancer. Therefore, its possible association with malignancy should be taken with care. To date, only 2 CT-directed prevalence studies performed a matched pair analysis to correct for potential confounding by age and sex [19, 59]. Following matched pair analyses, van Putte et al. found a significantly higher prevalence of malignancy (48,9 % vs. 46.3 %; $P < 0.05$) and metastasis (37 % vs. 26.4 %; $P < 0.05$) in SM patients at the time of the initial CT scan compared to the control group [59]. Prostatic carcinoma was the most frequent coexisting malignancy, which was also reported by others [7]. The chance of future cancer development during the 5-year follow-up period was also significantly higher in SM patients compared to that in the control group (14,6 % vs. 6,9 %; $P < 0.05$). Conversely, Gögebakan et al. did not find any relation between SM and malignancy in their matched pair analysis [19]. However, it is unclear whether extensive follow-up of the control group was performed in this study. In addition, follow-up imaging was available in only 35 of 77 SM patients [19]. In the study by van Putte et al. follow-up was performed in all SM and control patients during a 5-year period using information from follow-up imaging and medical records [59]. These and other findings suggesting an association with malignancy [19, 32, 63] indicate that SM may be relevant in terms of clinical predictivity of an associated neoplasm, particular for prostatic carcinoma. However, further study is needed to substantiate this point.

11.4.3 Previous Abdominal Surgery or Trauma

Previous abdominal surgery and associated intraabdominal pathology may have influenced the development of nonspecific inflammation in the adipose tissue. Percentage of SM patients who had previous abdominal surgery in large case series varies from 5 to 35 % (Table 11.1). Prevalence studies noted previous abdominal surgery for several conditions in up to 50 % of identified SM patients, with time interval from surgery to SM diagnosis varying from weeks to many years [59]. Besides direct trauma, use of powdered surgical gloves before the mid-1980s, retainement of suture material and abdominal hemorrhage are speculated to play a role in the development of SM [1, 13, 41, 42].

11.4.4 IgG4-Related Disease

In recent years, it is argued that in a subset of patients SM may be part of the spectrum of IgG4-RD, an immune-mediated disorder that may affect many different organs, notably pancreas, salivary glands, lacrimal glands and lungs [43, 54]. IgG4-RD is characterized by a lymphoplasmocytic infiltrate, predominantly consisting of IgG4-bearing plasma cells, storiform fibrosis, tissue eosinophilia and obliterative phlebitis. Concurrently raised serum levels of IgG4 are often seen, but low serum levels do not exclude the presence of IgG4-RD [43, 54]. Some cases of SM indeed have such histologic features and concomitant involvement at other sites, suggesting that these may be manifestations of IgG4-RD (see Sect. 11.5.2).

11.5 Pathology

11.5.1 Macroscopic Findings

The pathology of SM is usually limited to the mesentery of the small intestine and involves the root or a segment of the mesentery [15, 42]. The lesions are described as yellow/gray and hard with gritty consistency [15]. Typically, the lesions appear as diffuse thickening of the mesentery or as a single rubbery nodular mass or multiple masses [15, 42]. In addition, extensive scarring and shortening of the mesentery in addition to thickening may be observed [15, 42]. In rare cases, the omentum, mesoappendix, mesocolon, and large bowel mesentery may be involved [13, 15, 42]. The inflammatory process may extend to the retroperitoneum and involve the inferior vena cava, pancreas, duodenum, hepatic peduncle and bladder [1, 15, 42, 51].

Table 11.1 Major characteristics of patients with sclerosing mesenteritis

Characteristic	Durst [13]	Emory [15]	Akram [1]
Year of publication	1977	1997	2007
Study design	Cumulative literature data[a]	Retrospective, single-center[b]	Retrospective, single-center[c]
Study period	1955–1972	1970–1993	1982–2005
No. of cases	68	84	92
Age at diagnosis, *yr* (*range*)	53 (7–82)	60 (23–87)	Median 64.5 (IQR 55–72)
Male–female ratio	1.8:1	1.9:1	2.3:1
Previous abdominal surgery/ trauma, *n* (%)	12 (18)	4/78 (5)	32 (35)
Associated conditions, *n* (%)			
Rheumatologic disorders	N/A	1/78 (1.2)	5 (6)
Fibrosis at other sites	N/A[d]	4 (5)	4 (4)
Duration of symptoms, *mo* (*range*)	N/A (24 h to 2 years)	12 (days to 10 years)	N/A
Symptoms, *n* (%)			
Abdominal pain	46 (68)	27/78 (35)	65 (70)
Diarrhea or constipation	11 (16)	N/A	33 (41)
Bloating/distension	N/A	N/A	24 (26)
Weight loss	10 (15)	N/A	21 (23)
Nausea and vomiting	22 (32)	N/A	18 (21)
Fever	11 (16)	N/A	5 (6)
Physical examination, *n* (%)			
Palpable abdominal mass	34 (50)	24/78 (31)	14 (15)
Signs of bowel obstruction	22 (32)	24/78 (31)	22 (24)
Elevated ESR, *n* (%)	N/A	N/A	13 (14)
Concurrent other intra-abdominal pathology	17 (25)	N/A	17 (18)
Malignant disease	4 (6)	N/A	7 (8)
Nonmalignant disease	13 (19)	N/A	10 (10)

Unless noted otherwise, data are mean and range and counts and percentages
N/A not available
[a]Data collected from case reports and small case series in the literature and personal experience with six cases;
[b]Cases retrieved from the files of the Armed Forces Institute of Pathology, Washington, DC, USA; clinical information was available from 78 cases;
[c]Cases ($n=64$) were retrospectively identified through the Mayo Clinic Diagnostic Index and Department of Pathology database from the Mayo Clinic, Rochester, Minnesota, USA; 28 cases were prospectively identified as referrals to the gastroenterology outpatient department;
[d]Retroperitoneal extension of SM was noted in 7 cases (10%)

11.5.2 Microscopic Findings

The microscopic picture is that of a mild to moderate infiltration of the fat by macrophages with an abundant foamy cytoplasm [13, 15, 42]. The macrophages are distributed in thin and broad interconnecting bands. Focal collections of lymphocytes are seen, usually adjacent to small vessels and frequently without follicle formation with fewer plasma cells and scattered eosinophils [13, 15, 42]. Focal or multifocal venulitis and (obliterative) phlebitis may be observed, predominantly affecting small- to medium-sized venous channels and in rare cases large veins [6]. Polymorphonuclear leukocytes are uncommon. The mesenteric inflammatory process may progress to include necrosis, fibrosis and calcification [13, 15, 42]. A zone of lipid-laden macrophages oriented about a central lymphoid aggregate or lymph node with an interposed zone of normal fat may be seen, the so-called halo-effect [9]. In patients with cavitation, areas of amorph material containing cholesterol were present [13]. Depending on the predominant histologic appearance, it was thought that SM presented in three distinct and sequential histologic stages with accordingly appropriate and different naming of the disease: (1) the presence of lipid-laden foamy macrophages infiltrating the mesenteric fat, *mesenteric lipodystrophy*; (2) predominant chronic inflammatory infiltrate, *mesenteric panniculitis*; and (3) prominent fibrosis with scant inflammation and fat necrosis, *retractile mesenteritis/mesenteric fibrosis/sclerosing mesenteritis* [1, 13, 15, 42]. However, the diagnostic groups all share the presence of fibrosis, chronic inflammation and fat necrosis and, in addition, have common demographic and clinical characteristics [15]. Upon statistical analysis of the three major histologic components, the amount of fibrosis was found to be the main feature of the different stages. Hence, the term "sclerosing mesenteritis" was proposed as the most accurate naming of the disease in the majority of cases [15].

Immunohistochemical staining typically shows a mixed population of CD3-positive T cells and CD19/CD20-positive B cells. Keratin, S-100, bcl-2, CD117/c-kit immunostain and T-cell receptor gene rearrangement studies are all negative [1]. MDM-2 immunohistochemistry may differentiate SM from well-differentiated liposarcoma, negative MDM-2 immunoexpression essentially ruling out the latter [62]. The connection between SM and IgG4-RD has not been studied extensively [1, 4, 6, 38, 40]. Abundant tissue infiltration of IgG4-positive plasma cells was observed in 4 of 12 SM cases (33 %) [1]. In a pathologic study of tissue material from 9 SM patients, IgG4-reactive plasma cells ranged in number from 0 to >100 per hpf, in 4 cases IgG4-positivity of plasma cells being between 11 and 20 per hpf and in 2 cases >100 per hpf [6]. The ratio of IgG4-positive/IgG-positive plasma cells varied from 3 to >100 per hpf in 6 cases studied, in 3 of these 6 cases (50 %) being ≥60/hpf [6]. In a 82-year-old woman with SM [40], microscopic examination showed abundant stromal fibrosis and obstructive phlebitis. Numerous IgG4-positive plasma cells were observed with a IgG4/IgG ratio of

76 %. IgG4 serum level, examined post-surgery, was high. In another case report of a 53-year-old man with extensive SM, storiform fibrosis, obliterative phlebitis and infiltration of many IgG4-positive plasma cells was observed [38]. The IgG4/IgG ratio amounted to 64 %, and the ratio of forkhead box protein 3 (Foxp3)-positive/CD4-positive cells was elevated (13 %) [38]. Foxp3 + cells are typically observed in auto-immune pancreatitis (AIP), the most prominent manifestation of IgG4-RD and are a good marker of CD4 + CD25 + regulatory T cells, which are thought to participate in the pathogenesis of the IgG4 reaction in AIP [64, 65]. These combined findings suggest that in a subset of patients, SM may be a manifestation of IgG4-RD.

11.6 Clinical Characteristics

SM typically affects middle-aged to older adults and is twice as common in men (Table 11.1). The clinical manifestations are largely nonspecific. SM may be asymptomatic and diagnosed incidentally on CT examination for other indications. In symptomatic patients, duration of symptoms vary from 24 h to 10 years (Table 11.1). In our experience, SM may present as an acute disease with often raised acute-phase reactant levels and as a chronic disease with usually unremarkable laboratory investigation. This may relate to the predominant (histologic) stage of the disease, i.e., inflammation or fibrosis [13]. The most common symptom is abdominal pain, often accompanied by diarrhea or constipation, weight loss, nausea and vomiting (Table 11.1). There does not seem to be a specific abdominal pain locus and every quadrant can be affected. Although uncommon, fever may be present. Physical examination frequently reveals a palpable mass and may reveal signs of bowel obstruction (Table 11.1). Bowel obstruction typically involves the small bowel but focal large bowel obstruction may occur [1, 13]. In most patients however, physical examination is unremarkable but for local abdominal tenderness or abdominal distention [13, 15, 42]. In rare cases, SM is complicated by (chylous) ascites, gastrointestinal bleeding, superior mesenteric vein thrombosis, and pleural or pericardial effusion [13–15, 42].

11.7 Laboratory Findings

Laboratory investigation is usually unremarkable. There may be raised acute-phase reactant levels (Table 11.1), sometimes accompanied by mild anemia. Usually mild leukocytosis may be found in the absence of other inflammatory disease and occasionally, leucopenia may be seen [13, 42]. A raised serum IgG4 level is sometimes observed [40].

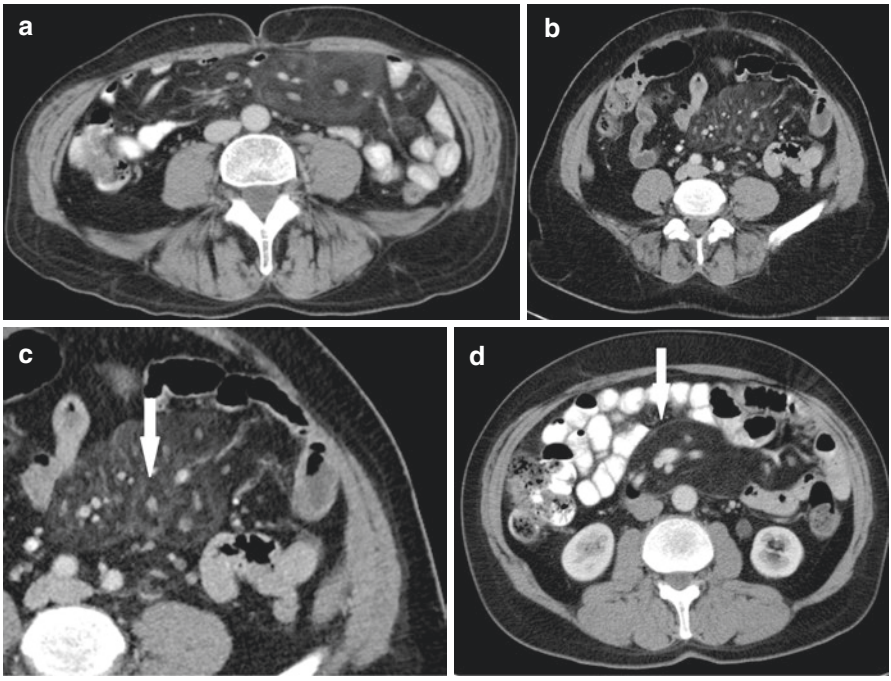

Fig. 11.1 (**a**): Sclerosing mesenteritis: the mesenteric fat is hyperdense compared to the subcutaneous or retroperitoneal fat and displaces surrounding small bowel loops. (**b**): Sclerosing mesenteritis in another patient. (**c**): Sclerosing mesenteritis with the characteristic "fat-ring" sign. The mesenteric vessels, which are surrounded by normal fat, are enveloped by hyperdense mesenteric fat. (**d**): Sclerosing mesenteritis with "tumoral pseudo-capsule", a dens stripe in the peripheral region differentiating normal mesentery from the inflammatory process

11.8 Imaging

11.8.1 Computed Tomography

Most cases of SM are asymptomatic and incidentally detected on abdominal CT examination. CT features vary from subtle increased attenuation (attenuation values of −40 to −60 Hounsfield Units [HU]) of the mesentery to a more solitary well-defined soft tissue mass at the root of the small bowel mesentery [7, 10, 24, 29]. There is engulfment of superior mesenteric vessels and displacement of the bowel loops without infiltration (Fig. 11.1a,b). Small lymph nodules (short axis <10 mm) are often seen within the region of mesenteric fat stranding. Typically, the mesenteric vessels and soft tissue nodes show a "fat-ring" sign (Fig. 11.1c), referring to preservation of fat nearest to the mesenteric vessels and nodes [24, 56, 61]. A "tumoral pseudocapsule" (Fig. 11.1d), a dense stripe in the peripheral region differentiating normal mesentery from the inflammatory process is also suggestive for SM [10, 48]. Although uncommon, calcifications may be seen [23, 34, 59]. Table 11.2 shows the prevalence of the main CT features of SM in two large studies [10, 59].

Table 11.2 CT features in patients with sclerosing mesenteritis

Variable	Daskalogiannaki [10]	Van Putte-Katier [59]
Number of patients, *n*	49	94
Prevalence sclerosing mesenteritis, *%*	0.6	2.5
Transverse diameter, *cm*	9.5 ± 1.4	9.5 ± 1.9
Orientation transverse diameter, *n* (%)		
Leftward	48 (98)	91 (96.8)
Rightward/central	1 (2)	3 (3.2)
Density mesenteric fat, *HU*	−54 ± 2	−56.8 ± 10.8
Density retroperitoneal fat, *HU*	−116 ± 9	−105,0 (8)
Density subcutaneous fat, *HU*	NA	−109.2 ± 6.7
Fat ring sign, *n* (%)	42 (85.7)	88 (93.6)
Density, *HU*	−106 ± 4	−105.5 (12)
Stripe or pseudocapsule, *n* (%)	29 (59.2)	53 (56.4)
Lymph nodes, *n* (%)		
None	10 (20.4)	2 (2.1)
<5 mm	39 (79.6)	81 (86.2)
5–10 mm	N/A	11 (11.7)
Calcifications, *n* (%)	N/A	4 (4.3)

Values are mean ± standard deviation, median and interquartile range or numbers and percentages, where appropriate
N/A not available

11.8.2 Other Imaging Techniques

Ultrasound may reveal a well-defined homogeneous hyperechoic (fatty) mass at the mesenteric root with in most cases a clear interface between the normal fat and the inflammatory fat in SM [46]. Ultrasound findings may be subtle, easily missed, and findings are nonspecific and may be seen in other conditions involving the mesentery [58]. Magnetic resonance imaging (MRI) findings are similar to the CT features. On MRI, a mesenteric mass is seen with intermediate signal intensity on T1-weighted images and with slightly higher signal intensity on T2-weighted images [27]. ^{18}Fluorodeoxyglucose-(FDG) positron emission tomography (PET) has been proven useful mainly for the differentiation between SM (not FDG-avid) and malignant mesenteric involvement (FDG-avid), especially in patients with tumoral or lymphomatous involvement of the mesentery. A negative PET scan has a high diagnostic accuracy in excluding lymphomatous or tumoral involvement of the mesentery [66].

11.9 Diagnosis (Including Differential Diagnosis)

A definite diagnosis of SM can only be made by biopsy and pathologic analysis; however the incidental and often asymptomatic nature does not justify biopsy in most cases. Diagnosis can be made by imaging features, especially CT examination

(see Sect. 11.8). The term SM is solely reserved for idiopathic inflammation leading to infiltration of the mesentery and must be differentiated from any alternative causes altering density of the mesenteric fat ("misty mesentery") [24, 37, 52, 56, 58]. This includes mesenteric edema, hemorrhage, inflammation (e.g., pancreatitis and other inflammatory diseases of the gastrointestinal tract), retroperitoneal fibrosis (RPF), and neoplasm involving the mesentery including lymphoma and primary mesenteric neoplasm. When fibrosis dominates in SM, imaging features may overlap with carcinoid tumors, desmoid tumors, and peritoneal carcinomatosis. Lymphoma is the most common tumor involving the mesentery and is a challenging differential diagnosis to exclude, particularly in the early stage when bulky lymphadenopathy may still be absent [24, 37]. The "halo sign" and pseudocapsule favors SM, but can be seen in lymphoma. Any lymphadenopathy outside the mesenteric regions favors early stage lymphoma. Lymphoma will not contain calcifications, unless previously treated [24]. The CT appearance of SM and carcinoid can be identical. Both can appear as an infiltrating mass in the root of the mesentery with desmoplastic reaction and calcifications [7, 23, 24]. The "halo sign" favors SM, a discrete enhancing bowel mass and hypervascular liver metastases favor carcinoid tumor.

11.10 Overlap with Other (Fibroinflammatory) Disorders

Concomitant RPF and sclerosing pancreatitis has occasionally been noted in SM patients, suggesting that SM may sometimes be part of multifocal fibrosis [1]. In addition, typical histopathologic and immunohistochemical features of IgG4-RD has been observed in some cases of SM (see Sect. 11.5.2). However, SM may extend per continuitatem into the retroperitoneal space to involve the (peri-) pancreatic region, where histologic features of autoimmune pancreatitis are not present [13, 51]. In our extensive experience with RPF patients, concomitant noncontiguous CT-documented SM was noted on several occasions. Of interest, smoking has been linked to the development of both SM and RPF [12, 20].

11.11 Treatment and Prognosis

11.11.1 General Approach

The aims of treatment of SM are to relieve gastrointestinal symptoms, to relieve bowel obstruction if present, to induce regression of the fibroinflammatory reaction, and to avoid recurrence. Treatment should be guided by the severity of signs and symptoms and may include different drugs, surgical procedures, or both. Of note, many patients often have only mild symptoms, and SM may even be an incidental finding in otherwise asymptomatic patients. Medical treatment is usually not warranted for these patients. A novel nonpharmacological treatment option for cases refractory to medical treatment may be (repeated) endoscopic ultrasonography-guided celiac plexus block [2].

11.11.2 Surgical Treatment

The primary surgical approach should be limited to exploration with biopsy and, in cases of intractable bowel obstruction, palliative colostomy or bypass [1, 13, 15, 42]. In some cases, partial or complete resection of the mesenteric mass with the adjacent bowel may be possible [1, 42]. However, resection may be hazardous and often not feasible because of extensive encasement of the bowel or mesenteric blood vessels [1, 13, 15]. In addition, attempted surgical resection or debulking usually does not result in resolution of symptoms [1]. In some cases, segmental bowel resection may be required as a result of severe vascular compromise from the affected mesentery [1]. In case of coexistent intraabdominal diseases, additional surgical procedures may be needed [1, 42].

11.11.3 Medical Treatment

The medical treatment of SM is empiric and various pharmacological agents have been used to treat the disease. Already in the 1950s, treatment directed at the presumed inflammatory component was used with corticosteroids and azathioprine, either alone or combined [3, 42, 55]. Anecdotal case reports have described the use of cyclophosphamide [5], but we do not advocate its use because of the associated increased risk of infection, especially sepsis. Over the last decades, several other drugs have been used in the treatment of SM, notably tamoxifen (TMX) [1, 21, 35, 51, 60], colchicine [16, 17, 25], and thalidomide [1, 18]. Although often used in conjunction with other agents, notably corticosteroids, TMX has also been used successfully as monotherapy [21]. TMX down-regulates growth factors involved in fibroblast proliferation, has anti-inflammatory and immunomodulatory effects, and has antiangiogenic properties [21, 57]. We have also treated several SM patients successfully with TMX monotherapy (20 mg b.i.d.), with amelerioration of symptoms and CT-documented improvement at follow-up (Fig. 11.2). Adding colchicine to corticosteroid treatment allowed for tapering of steroids in previously steroid-dependent cases with maintenance of clinical remission [16, 25, 27]. Colchicine is thought to act through downregulation of inflammation and modulation of innate immunity. It also has antifibrotic activities and various effects on endothelial function [33]. Thalidomide has potent anti-inflammatory, immunomodulatory, and anti-angiogenic properties and suppresses TNF-α [18]. In an open-label pilot study, five patients with symptomatic SM received oral thalidomide (200 mg nightly) for 12 weeks. Thalidomide was well tolerated and symptoms ameliorated in four of the five patients (80 %) within this period with concurrent decrease in acute-phase reactant levels and stable mass at CT follow-up [18]. In a case of refractory symptomatic SM, despite steroid and azathioprine treatment, anti-TNFα therapy (Infliximab®) led to dramatic clinical as well as (subsequent) radiological improvement [47]. Recently, low-dose naltrexone proved useful in patients with symptomatic SM [45].

Given the paucity of published data on medical treatment of SM in larger case series and the absence of a direct comparison of different agents, it is hard to assess

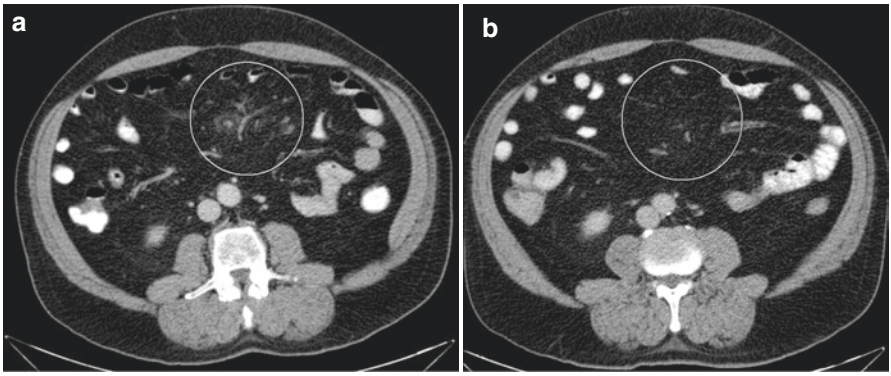

Fig. 11.2 (**a**): Contrast-enhanced abdominal CT scan in a 64-year-old man with chronic pain in the lower left abdomen and postprandial diarrhea showing discrete sclerosing mesenteritis. (**b**): Follow-up CT scan after 4 months of tamoxifen treatment (20 mg b.i.d.) showing complete disappearance of intraabdominal abnormalities. His symptoms had resolved within 4 weeks of treatment

the "true" success rate of different treatment regimens. The retrospective study of Akram et al. gives us a good impression as to the overall effect of different treatment regimens in SM [1]. From analyzing their data of individual patients receiving medical therapy without surgical intervention we constructed Table 11.3.[2] Overall, the disease was responsive to medical treatment in 9 of 22 patients (41 %). Data suggest that corticosteroids alone may not be sufficient to treat the disease. However, treatment regimens which included both initial high-dose prednisone and TMX proved successful in 8 of 12 cases (75 %) (Table 11.3). In these 12 cases, mean (initial) dose and duration of prednisone amounted to 38 (range 10–60) mg/day for 10 (range 2–24) months and of TMX 19 (range 10–20) mg/day for 24 (range 4–33) months. From the study it could not be derived if and to what extent CT-documented improvement was observed following treatment initiation in these patients. Persistent to progressive disease was seen more often in patients who did not receive medical treatment post-surgery compared to those who received additional medical treatment post-surgery (8/10 vs. 4/8 patients) [1]. Based on above mentioned data and our own experience, we suggest that medical treatment should be individualized according to presentation and severity of disease. As the disease usually has a benign course and may resolve spontaneously, medical treatment should usually not be offered to asymptomatic or mildly symptomatic patients. In patients with uncomplicated SM who are moderately symptomatic, TMX monotherapy (20 mg b.i.d.) may suffice as first-line therapy. Note that this dose is higher than used by others [1,

[2] From their study [1], we analyzed data of individual patients receiving medical treatment without surgical intervention with follow-up ≥ one month and categorized patients according to four different treatment regimens. Per treatment category we calculated the number of patients, mean age (y), male sex (*n*), response rate (*n*, %) and mean follow-up (range). We also calculated dose range per drug and mean (initial) dose (mg/day) and duration (month) of prednisone and tamoxifen in those patients who received medical treatment including both prednisone and tamoxifen.

Table 11.3 Results of medical treatment without surgical intervention in patients with sclerosing mesenteritis[a]

Medical treatment	Patients, *n*	Mean age, y/ male sex, *n*	Response to therapy			Follow-up, *mo*
			Responsive[b], *n* (%)	Persistent, *n* (%)	Progressive, *n* (%)	
PDN	6	64/4	0 (0)	4 (67)	2 (33)	25 (4–46)
PDN/TMX	9	70/7	5 (56)	3 (33)	1 (11)	30 (10–89)
PDN/ TMX + AZA/Col	3	63/0	3 (100)	0 (0)	0 (0)	19 (3–41)
Miscellaneous[c]	4	59/4	1 (25)	2 (50)	1 (25)	21 (8–60)
All treatment	22	66/15	9 (41)	9 (41)	4 (18)	26 (3–89)

Values are counts and percentages or mean and range, where appropriate
Abbreviations: *AZA* azathioprine (range 50–100 mg/day), *Col*, colchicine (range 1.2–1.8 mg/day), *PDN* initial high-dose prednisone/prednisolone (range 10–60 mg/day), *TMX* tamoxifen (range 10–20 mg/day)
[a]Table constructed from analyses of individual patient data from Akram et al. [1]
[b]Response to treatment was assessed by symptom evaluation and abdominal CT scanning at follow-up
[c]Treatment included TMX ($n=1$), TMX/C ($n=1$) or combined PDN/A with thalidomide ($n=1$) or colchicine ($n=1$)

21, 51, 60]. Extrapolating our results with TMX in RPF [57], we advocate long-term use of this fixed-dose regimen for up to 2 years in patients with satisfactory initial response. TMX is usually well tolerated with few side effects, albeit with an increased risk of thromboembolic events [57]. In patients with severe symptoms and/or signs of bowel obstruction, a trial with more aggressive therapy with combined TMX (20 mg b.i.d.) and initial high-dose corticosteroids (40–60 mg) seems appropriate. In responsive patients, corticosteroids can be tapered and discontinued after 6–12 months with continued long-term use of TMX. In refractory cases or intolerance/contraindications for corticosteroids or TMX, colchicine (1–2 mg/day) may be added. Thalidomide, anti-TNF therapy, and naltrexone should probably be withheld as "rescue" therapy until more data are available.

11.11.4 Prognosis

Because of the rarity of SM and the paucity of long-term follow-up data in larger patient groups, its natural course remains unclear. However, it does seem to have a benign course in most cases with little chance of recurrence, often with stable radiological abnormalities. Spontaneous resolvement of the mesenteric mass has been reported anecdotally [11, 22, 36]. Many cases therefore do not require any treatment. In some cases, however, it may be associated with significant morbidity and

a chronic debilitating course [1, 3, 13, 15]. Although rare, death from recurrent SM-related complications and its (surgical) sequelae has been reported [13, 15, 28, 31]. Overall mortality in larger case series of SM patients with long-term follow-up varied from 20 to 45 %, death usually being unrelated to SM [1, 15]. An important issue is whether follow-up in patients with SM should include repeat abdominal CT scanning. Some suggest that treatment is best assessed by symptomatic improvement alone [1]. However, it is unknown if clinical improvement with stable radiological abnormalities following treatment ultimately has another prognosis (e.g., chance of recurrence) than patients who have both clinical and radiological improvement at follow-up. Although further study is needed, SM may be a paraneoplastic phenomenon. We argue that CT follow-up is therefore justified, but proposing its frequency and timing is difficult and should probably be guided by SM-related and other signs and symptoms during follow-up.

Conclusions

SM is a rare disease characterized by chronic, nonspecific inflammation of the adipose tissue of the mesentery of the small intestine. Although several potential etiologic factors have been identified, its precise etiopathogenesis remains obscure. After careful age-appropriate cancer screening, a diagnosis of SM can be made with near-certainty with abdominal CT scanning, thereby obviating the need for routine biopsy. Although unproven, physicians should keep in mind that SM may be associated with (future) malignancy and other chronic (fibro) inflammatory disorders. Its course is usually favorable but severe complications may occur, notably bowel obstruction. Medical treatment should be offered to patients with moderate to severe symptoms, surgery usually being confined to palliative bypass in cases of bowel obstruction. Long-term follow-up is indicated.

References

1. Akram S, Pardi DS, Schaffner JA, Smyrk TC (2007) Sclerosing mesenteritis: clinical features, treatment, and outcome in ninety-two patients. Clin Gastroenterol Hepatol 5(5):589–596
2. Alhazzani W, Al-Shamsi HO, Greenwald E, Radhi J, Tse F (2015) Chronic abdominal pain secondary to mesenteric panniculitis treated successfully with endoscopic ultrasonography-guided celiac plexus block: a case report. World J Gastrointest Endosc 7(5):563–566. doi:10.4253/wjge.v7.i5.56
3. Bala A, Coderre SP, Johnson DR, Nayak V (2001) Treatment of sclerosing mesenteritis with corticosteroids and azathioprine. Can J Gastroenterol 15(8):533–535
4. Belghiti H, Cazals-Hatem D, Couvelard A, Guedj N, Bedossa P (2009) Sclerosing mesenteritis: can it be a IgG4 dysimmune disease? Ann Pathol 29(6):468–474
5. Bush RW, Hammar SP Jr, Rudolph RH (1986) Sclerosing mesenteritis. Response to cyclophosphamide. Arch Intern Med 146(3):503–505
6. Chen TS, Montgomery EA (2008) Are tumefactive lesions classified as sclerosing mesenteritis a subset of IgG4-related sclerosing disorders? J Clin Pathol 61(10):1093–1097
7. Coulier B (2011) Mesenteric panniculitis. Part 1: MDCT--pictorial review. JBR–BTR 94(5):229–240
8. Coulier B (2011) Mesenteric panniculitis. Part 2: prevalence and natural course: MDCT prospective study. JBR–BTR 94(5):241–246

9. Crane JT, Aguilar MJ, Grimes OF (1955) Isolated lipodystrophy, a form of mesenteric tumor. Am J Surg 90(2):169–179
10. Daskalogiannaki M, Voloudaki A, Prassopoulos P, Magkanas E, Stefanaki K, Apostolaki E et al (2000) CT evaluation of mesenteric panniculitis: prevalence and associated diseases. Am J Roentgenol 174(2):427–431
11. Daumas A, Agostini S, Villeret J, Ah-Soune P, Emungania O, Granel B (2012) Spontaneous resolution of severe, symptomatic mesocolic panniculitis: a case report. BMC Gastroenterol 12:59
12. Delgado Plasencia L, Rodríguez Ballester L, López-Tomassetti Fernández EM, Hernández Morales A, Carrillo Pallarés A, Hernández Siverio N (2007) Mesenteric panniculitis: experience in our center. Rev Esp Enferm Dig 99(5):291–297
13. Durst AL, Freund H, Rosenmann E, Birnbaum D (1977) Mesenteric panniculitis: review of the literature and presentation of cases. Surgery 81(2):203–211
14. Ehrenpreis ED, Boiskin I, Schaefer K (2008) Chylous ascites in a patient with mesenteric panniculits. J Clin Gastroenterol 42(3):327–328
15. Emory TS, Monihan JM, Carr NJ, Sobin LH (1997) Sclerosing mesenteritis, mesenteric panniculitis and mesenteric lipodystrophy: a single entity? Am J Surg Pathol 21(4):392–398
16. Fasoulas K, Beltsis A, Katsinelos T, Dimou E, Arvaniti M, Charsoula A et al (2012) Efficacy of colchicine in the treatment of mesenteric panniculitis in a young patient. Saudi J Gastroenterol 18(2):146–148
17. Genereau T, Bellin MF, Wechsler B, Le TH, Bellanger J, Grellet J et al (1996) Demonstration of efficacy of combining corticosteroids and colchicine in two patients with idiopathic sclerosing mesenteritis. Dig Dis Sci 41(4):684–688
18. Ginsburg PM, Ehrenpreis ED (2002) A pilot study of thalidomide for patients with symptomatic mesenteric panniculitis. Aliment Pharmacol Ther 16(12):2115–2122
19. Gögebakan O, Albrecht T, Osterhoff MA, Reimann A (2013) Is mesenteric panniculitis truely a paraneoplastic phenomenon? A matched pair analysis. Eur J Radiol 82(11):1853–1859
20. Goldoni M, Bonini S, Urban ML, Palmisano A, De Palma G, Galletti E et al (2014) Asbestos and smoking as risk factors for idiopathic retroperitoneal fibrosis: a case-control study. Ann Intern Med 161(3):181–188
21. Gottschalk U, Nitzsche C, Felber J, Dietrich CF (2012) Enteroscopy and imaging in sclerosing mesenteritis. Z Gastroenterol 50(9):1013–1017
22. Hasbahçecı M, Başak F, Seker M, Canbak T, Kiliç A, Alımoğlu O (2012) Spontaneous remission of sclerosing mesenteritis. Turk J Gastroenterol 23(4):378–380
23. Hemaidan A, Vanegas F, Alvarez OA, Arroyo MA, Lee M (1999) Mesenteric lipodystrophy with fever of unknown origin and mesenteric calcifications. South Med J 92(5):513–516
24. Horton KM, Lawler LP, Fishman EK (2003) CT findings in sclerosing mesenteritis (panniculitis): spectrum of disease. Radiographics 23(6):1561–1567
25. Iwanicki-Caron I, Savoye G, Legros JR, Savoye-Collet C, Herve S, Lerebours E (2006) Successful management of symptoms of steroid-dependent mesenteric panniculitis with colchicine. Dig Dis Sci 51(7):1245–1249
26. Jura V (1924) Sulla mesenterite retrattile e sclerosante. Policlinico (Sez Chir) 31:575
27. Kakitsubata Y, Umemura Y, Kakitsubata S, Tamura S, Watanabe K, Abe Y et al (1993) CT and MRI manifestations of intraabdominal panniculitis. Clin Imaging 17(3):186–188
28. Katsanos KH, Ioachim E, Michail M, Price AC, Agnantis N, Kappas A et al (2004) A fatal case of sclerosing mesenteritis. Dig Liver Dis 36(2):153–156
29. Katz ME, Heiken JP, Glazer HS, Lee JK (1985) Intraabdominal panniculitis: clinical, radiographic, and CT features. Am J Roentgenol 145(2):293–296
30. Kelly JK, Hwang WS (1989) Idiopathic retractile (sclerosing) mesenteritis and its differential diagnosis. Am J Surg Pathol 13(6):513–521
31. Kida T, Suzuki K, Matsuyama T, Okita M, Isozaki Y, Matsumoto N et al (2011) Sclerosing mesenteritis presenting as protein-losing enteropathy: a fatal case. Intern Med 50(22):2845–2849
32. Kipfer RE, Moertel CG, Dahlin DC (1974) Mesenteric lipodystrophy. Ann Intern Med 80(5):582–588

33. Leung YY, Yao Hui LL, Kraus VB (2015) Colchicine-Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum. pii: S0049-0172(15)00179-1
34. Mata JM, Inaraja L, Martin J, Olazabal A, Castilla MT (1987) CT features of mesenteric panniculitis. J Comput Assist Tomogr 11(6):1021–1023
35. Mazure R, Fernandez MP, Niveloni S, Pedreira S, Vazquez H, Smecuol E et al (1998) Successful treatment of retractile mesenteritis with oral progesterone. Gastroenterology 114(6):1313–1317
36. McCormack O, Meaney JF, Reynolds JV (2013) Resolving sclerosing mesenteritis. Surgery 153(6):879–880
37. McLauglin PD, Filippone A, Maher MM (2013) The "misty mesentery": mesenteric panniculitid and its mimics. AJR Am J Roentgenol 200(2):W116–W123
38. Minato H, Shimizu J, Arano Y, Saito K, Masunaga T, Sakashita T, Nojima T (2012) IgG4-related sclerosing mesenteritis: a rare mesenteric disease of unknown etiology. Pathol Int 62(4):281–286
39. Nicholson JA, Smith D, Diab M, Scott MH (2010) Mesenteric panniculitis in Merseyside: a case series and a review of the literature. Ann R Coll Surg Engl 92(6):W31–W34
40. Nomura Y, Naito Y, Eriguchi N, Kume T, Itai N, Sonoda H et al (2011) A case of IgG4-related sclerosing mesenteritis. Pathol Res Pract 207(8):518–521
41. Ogden WW, Bradburn DM, Rives JD (1960) Panniculitis of the mesentery. Ann Surg 151:659–668
42. Ogden WW, Bradburn DM, Rives JD (1965) Mesenteric pannicultitis: review of 27 cases. Ann Surg 161:864–875
43. Okazaki K, Uchida K, Miyoshi H, Ikeura T, Takaoka M, Nishio A (2011) Recent concepts of autoimmune pancreatitis and IgG4-related disease. Clin Rev Allergy Immunol 41(2):126–138
44. Parra-Davila E, McKenney MG, Sleeman D, Hartmann R, Rao RK, McKenney K et al (1998) Mesenteric panniculitis: case report and literature review. Am Surg 64(8):768–771
45. Roginsky G, Alexoff A, Ehrenpreis ED (2015) Initial findings of an open-label trial of low-dose naltrexone for symptomatic mesenteric panniculitis. J Clin Gastroenterol 49(9):794–795. doi:10.1097/MCG.0000000000000398
46. Rosón N, Garriga V, Cuadrado M, Pruna X, Carbó S, Vizcaya S, Peralta A, Martinez M, Zarcero M, Medrano S (2006) Sonographic findings of mesenteric panniculitis: correlation with CT and literature review. J Clin Ultrasound 34(4):169–176
47. Rothlein LR, Shaheen AW, Vavalle JP, Smith SV, Renner JB, Shaheen NJ, Tarrant TK (2010) Sclerosing mesenteritis successfully treated with a TNF antagonist. BMJ Case Rep 2010:bcr0720103145. doi:10.1136/bcr.07.2010.3145
48. Sabate JM, Torrubia S, Maideu J, Franquet T, Monill JM, Perez C (1999) Sclerosing mesenteritis: imaging findings in 17 patients. Am J Roentgenol 172(3):625–629
49. Salvarani C, Valli R, Boiardi L, Pipitone N, Nicoli F, Muratore F (2011) IgG4-associated sclerosing mesenteritis. Clin Exp Rheumatol 29(1 Suppl 64):S79–S80
50. Schaffler A, Scholmerich J, Buchler C (2005) Mechanisms of disease: adipocytokines and visceral adipose tissue--emerging role in intestinal and mesenteric diseases. Nat Clin Pract Gastroenterol Hepatol 2(2):103–111
51. Scudiere JR, Shi C, Hruban RH, Herman JM, Fishman EK, Schulick RD et al (2010) Sclerosing mesenteritis involving the pancreas: a mimicker of pancreatic cancer. Am J Surg Pathol 34(4):447–453
52. Seo BK, Ha HK, Kim AY, Kim TK, Kim MJ, Byun JH et al (2003) Segmental misty mesentery: analysis of CT features and primary causes. Radiology 226(1):86–94
53. Smith ZL, Sifuentes H, Deepak P, Ecanow DB, Ehrenpreis ED (2013) Relationship between mesenteric abnormalities on computed tomography and malignancy: clinical findings and outcomes of 359 patients. J Clin Gastroenterol 47(5):409–414
54. Stone JH (2012) IgG4-related disease: nomenclature, clinical features, and treatment. Semin Diagn Pathol 29(4):177–190

55. Tytgat GN, Roozendaal K, Winter W, Esseveld MR (1980) Successful treatment of a patient with retractile mesenteritis with prednisone and azathioprine. Gastroenterology 79(2):352–356
56. Valls C (2000) Fat-ring sign in sclerosing mesenteritis. Am J Roentgenol 174(1):259–260
57. Van Bommel EF, Pelkmans LG, Van DH, Hendriksz TR (2013) Long-term safety and efficacy of a tamoxifen-based treatment strategy for idiopathic retroperitoneal fibrosis. Eur J Intern Med 24(5):444–450
58. Van Breda-Vriesman AC, Schuttevaer HM, Coerkamp EG, Puylaert JB (2004) Mesenteric panniculitis: US and CT features. Eur Radiol 14(12):2242–2248
59. Van Putte-Katier N, van Bommel EF, Elgersma OE, Hendriksz TR (2014) Mesenteric panniculitis: prevalence, clinicoradiological presentation and 5-year follow-up. Br J Radiol 87(1044):20140451
60. Venkataramani A, Behling CA, Lyche KD (1997) Sclerosing mesenteritis: an unusual cause of abdominal pain in an HIV-positive patient. Am J Gastroenterol 92(6):1059–1060
61. Wat S, Harish S, Winterbottom A, Choudhary AK, Freeman AH (2006) The CT appearances of sclerosing mesenteries and associated diseases. Clin Radiol 61:652–658
62. Weaver J, Goldblum JR, Turner S, Tubbs RR, Wang WL, Lazar AJ, Rubin BP (2009) Detection of MDM2 gene amplification or protein expression distinguishes sclerosing mesenteritis and retroperitoneal fibrosis from inflammatory well-differentiated liposarcoma. Mod Pathol 22(1):66–70
63. Wilkes A, Griffin N, Dixon L, Dobbs B, Frizelle FA (2012) Mesenteric panniculitis: a paraneoplastic phenomenon? Dis Colon Rectum 55(7):806–809
64. Zen Y, Fujii T, Harada K et al (2007) Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. Hepatology 45:1538–1546
65. Zhao LN, Han WY, Lu L, Yu T, Li JY, Min XH et al (2014) Clinical features and expressions of Foxp3 and IL-17 in type 1 autoimmune pancreatitis in China. Med Sci Monit 20:2720–2728
66. Zissin R, Metser U, Hain D, Even-Sapir E (2006) Mesenteric panniculitis in oncologic patients: PET-CT findings. Br J Radiol 79(397):37–43