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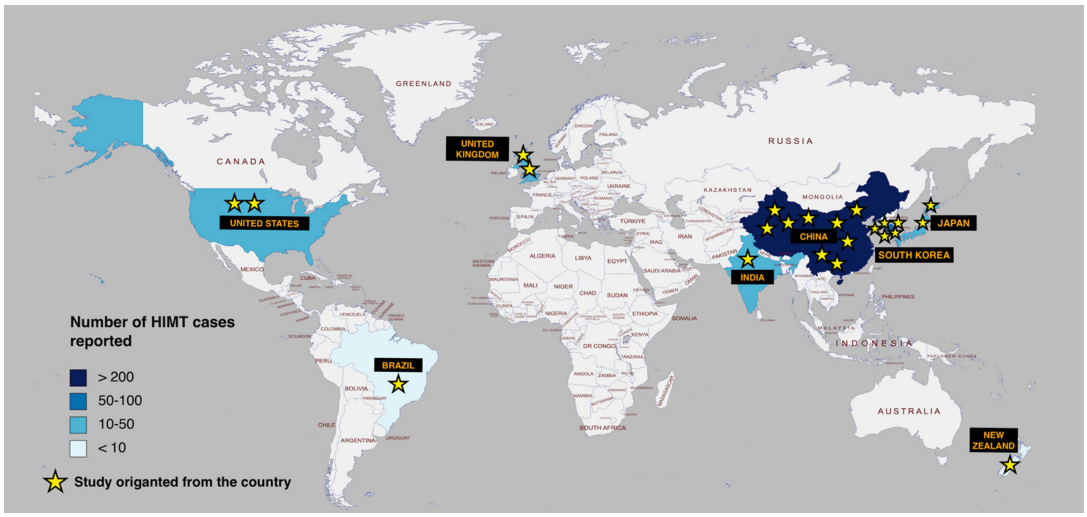
Inflammatory myofibroblastic tumours of the liver – a systematic review

Supplementary files



Supplementary Figure 1: Country distribution of the included studies (Created on: https://www.mapchart.net/world.html.)

Supplementary Table I: Advanced search strategy for PubMed (Medline) and other databases

#	Field	Search Term
#1	MeSH Terms	liver*
#2	Title/Abstract	inflammatory myofibroblastic tumour
#3	Title/Abstract	inflammatory pseudotumour
#4	MeSH Terms	granuloma, plasma cell
#5	Title/Abstract	inflammatory fibrosarcoma
#6	Title/Abstract	post-inflammatory tumour
#7	Title/Abstract	xanthomatous pseudotumour
#8	Title/Abstract	sclerosing pseudotumour
#9		#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10		#1 AND #9
#11	Filter	humans
#12		#10 AND #11

*The strategy was modified to obtain optimal searching results in different database search engines.

Supplementary Table II: Study characteristics and patient baseline clinical presentations and biochemical results

First author, year	Country of origin	Patients (*n*)	Gender of patients	Age	Clinical presentations (*n*)	Biochemical results *n* (%)		
						Hepatitis B+	Leukocytosis	Tumour marker elevation
Calomeni, 2013[17]	Brazil	4	Male: 3 Female: 1	54.3 ± 18.7*	Abdominal pain / discomfort (3) Fever (2) Hepatomegaly (1) Haemobilia (1) Jaundice (1) Weight loss (1)	0 (0)	1 (25)	NR
Li,1989[22]	China	4	Male: 3 Female: 1	42.0 ± 13.0*	Abdominal pain / discomfort (4) Fever (1)	NR	1 (25)	AFP: 1 (25) 1080 ng/mL
Qiu, 2013[23]	China	9	Male: 7 Female: 2	49.5 (41–65)**	Abdominal pain / discomfort (8) Weight loss / anorexia (4) Fever (2)	1 (11.1)	2 (22.2)	AFP: 1 (11.1)
Yang, 2014[24]	China	11	Male: 7 Female: 4	45.8 ± 14.4*	Fever / Chills (8) Abdominal pain / discomfort (4) Nause-Vomiting (1) Back pain (1) Asymptomatic (2)	2 (18.2)	3 (27.3)	AFP: 1 (9.1) 98.78 ng/mL
Tang, 2010[25]	China	64	Male: 42 Female: 22	49.1 ± 12.5*	Abdominal pain / discomfort (40) Fever (26) Malaise (13) Jaundice (4) Weight loss (2) Asymptomatic (10)	25 (39.1)	NR	NR
Yang, 2015[11]	China	114	Male: 69 Female: 45	53.1 ± 11.0*	Abdominal pain / discomfort (94) Fever (48) Nause / vomiting (29) Weight loss (12) Malaise (10)	18 (15.8)	NR	NR
Gao, 2023[26]	China	15	Male: 11 Female: 4	51.1 ± 8.7*	Abdominal pain / discomfort (5) Fever (3) Asymptomatic (7)	3 (20)	2 (13.3)	CA 19-9: 1 (6.7) 84.9 U/mL
Tsou, 2006[27]	China	8	Male: 4 Female: 4	59.5 ± 15.2*	Abdominal pain / discomfort (5) Fever (3) Jaundice (3) Weight loss (3) Malaise (1)	1 (12.5)	5 (62.5)	CA 19-9: 3 (75) 79.7 U/mL, 117.92 U/mL, 842 U/mL
Xiao, 2013[28]	China	9	Male: 4 Female: 5	50.7 ± 11.0*	Abdominal pain / discomfort (7) Fever (6) Weight loss (4) Jaundice (2) Asymptomatic (1)	0 (0)	NR	NR

Supplementary Table II: Continued

First author, year	Country of origin	Patients (*n*)	Gender of patients	Age	Clinical presentations (*n*)	Biochemical results *n* (%)		
						Hepatitis B+	Leukocytosis	Tumour marker elevation
Liang, 2014[29]	China	24	Male: 21 Female: 3	47.8 ± 15.4*	Fever (16) Abdominal pain / discomfort (4) Asymptomatic (6)	11 (45.8)	1 (4.2)	CA 19-9: 2 (8.3) 62.39 U/mL, 101.73 U/mL
Nigam, 2019[30]	India	17	Male: 11 Female: 6	47.2 ± 11.2*	Fever (10) Weight loss / anorexia (9) Abdominal pain / discomfort (8) Nause / vomiting (5) Jaundice (4)	NR	8 (47)	CA 19-9: 2 (13.3) 518.8 U/mL, 147.4 U/mL
Ijuin, 1997[31]	Japan	8	Male: 2 Female: 6	57.9 ± 10.4*	Fever (5) Weight loss (1) Malaise (1)	1 (12.5)	NR	NR
Horiuchi, 1990[32]	Japan	8	Male:7 Female: 1	51.0 ± 18.1*	Fever (6) Abdominal pain / discomfort (5) Weight loss (1) Diarrhea (2) Jaundice (2)	NR	7 (87.5)	NR
Yoon, 1999[12]	Korea	10	Male: 5 Female: 5	52.2 ± 10.1*	Fever (8) Abdominal pain / discomfort (7) Indigestion (4) Weight loss (1)	NR	3 (30)	NR
Kang, 2013[33]	Korea	13	Male: 10 Female: 3	55.8 ± 10.6*	Fever (3) Abdominal pain / discomfort (1) Asymptomatic (9)	NR	2 (15.4)	AFP: 1 (8.3) 5630.3 ng/mL
Ahn, 2011[34]	Korea	22	Male: 16 Female: 6	59.4 ± 9.9*	Abdominal pain / discomfort (12) Fever (5) Malaise (1) Asymptomatic (4)	1 (4.5)	6 (27.3)	AFP: 1 (4.5) 106.5 ng/mL CA19-9: 4 (18.2) 45.42 U/mL, 67.85 U/mL, 76.43 U/mL, 360.5 U/mL
Park, 2014[35]	Korea	45	Male: 26 Female: 19	65.0 (29-84)***	Abdominal pain / discomfort (16) Fever (11) Malaise (5) Weight loss (4) Asymptomatic (9)	4 (8.9)	10 (22.2)	AFP: 1 (2.2) CEA: 1 (2.2) CA 19-9: 1 (2.2)
Oh, 2021[13]	Korea	7	Male: 5 Female: 2	62.3 ± 11.6*	Abdominal pain / discomfort (16) Fever (11) Malaise (5) Weight loss (4)	4 (57.1)	NR	NR

Supplementary Table II: Continued

First author, year	Country of origin	Patients (*n*)	Gender of patients	Age	Clinical presentations (*n*)	Biochemical results *n* (%)		
						Hepatitis B+	Leukocytosis	Tumour marker elevation
Koea, 2003[36]	New Zealand	5	Male: 4 Female: 1	45.8 ± 22.8*	Fever (3) Abdominal pain / discomfort (2) Weight loss (2) Malaise (1) Indigestion (1) Asymptomatic (1)	1 (20)	3 (60)	NR
Milias, 2009[37]	UK	4	Male: 2 Female: 2	53.3 ± 16.9*	Abdominal pain / discomfort (4) Fever (2) Malaise (2) Nause / vomiting (1) Jaundice (1) Pruritus (1)	NR	4 (100)	NR
Stoll, 2010[38]	US	9	Male: 6 Female: 3	65.3 ± 14.1*	Abdominal pain / discomfort (2) Shortness of breath (1) Fever (1) Asymptomatic (4)	NR	NR	NR
Arora, 2021[39]	US & UK	30	Male: 14 Female: 16	56.8 ± 16.0*	Abdominal pain / discomfort (14) Fever (8)	NR	NR	NR

NR – Not reported,
* Mean age (± SD), ** Median age (range),
*** Mean age (range)

Supplementary Table III: Imaging features and histopathological characteristics

First author, year	Imaging features				Histopathological characteristics		
	Solitary / Multiple (*n*)	CT *n* (%)	US *n* (%)	MRI *n* (%)	Liver biopsy *n* (%)	Immunohistochemistry (IHC) (*n*)	Microscopic appearance
Calomeni, 2013[17]	Solitary (4)	4 (100)	2 (50)	NR	NR	NR	Fibroblastic proliferation with infiltration of plasma cells, lymphocytes, and histiocytes
Li,1989[22]	Solitary (4)	4 (100)	4 (100)	NR	NR	NR	Infiltration of plasma cells, histiocytes, and fibroblasts.
Qiu, 2013[23]	Solitary (9)	9 (100) Precontrasted: Irregular, hypodense lesions with poorly defined margins Contrasted: Marginal enhancement on the delayed phase Mild enhancement on the arterial phase	9 (100) Hypoechogenic	2 (22.2) Hypointense on T1WI Isointense or hyperintense on T2WI	1 (11.1)	NR	NR
Yang, 2014[24]	Solitary (8) Multiple (3)	7 (63.6) Precontrasted: Hypodense lesions Contrasted: Peripheral enhancement on the delayed phase	10 (90.9) Hypoechogenic solid mass	Heterogeneous, mild isointense, or hypointense on T1WI Hypointense center with hyperintense rim on T2WI	1 (9.1)	SMA+ (9) Vimentin+ (3) CD68+ (2) IgG4+ (1)	Fibroblastic proliferation with infiltration of plasma cells, lymphocytes, and/or eosinophils
Tang, 2010[25]	Solitary (50) Multiple (14)	44 (68.8) Contrasted: Peripheral or heterogeneous enhancement	64 (100)	31 (48.4) Hypointense on T1WI Hyperintense on T2WI Heterogeneous or peripheral enhancement on Gadolinium-enhanced images	NR	Vimentin+ (64) SMA+ (57) Desmin+ (41) CD68+ (38)	Fibroblastic proliferation with infiltration of inflammatory cells OR with myxoid, vascular, and inflammatory areas
Yang, 2015[11]	Solitary (110) Multiple (4)	40 (35.1) Precontrasted: Hypodense lesions with well-defined margins. Contrasted: Inhomogeneous enhancement on the arterial phase	107 (93.9) Mixed echogenicity	46 (40.3) Hypointense on T1WI Isointense on T2WI	NR	NR	Inflammatory cells with infiltration of predominantly plasma cells and eosinophil
Gao, 2023[26]	Solitary (11) Multiple (4)	3 (20) FDG-PET/ CT: FDG avid	NR	NR	8 (53.3)	Vimentin+ (11) SMA+ (11) CD68+ (4) CD3+ (4)	Fibroblastic proliferation with infiltration of lymphocytes and plasma cells

Supplementary Table III: Continued

First author, year	Imaging features				Histopathological characteristics		
	Solitary / Multiple (*n*)	CT *n* (%)	US *n* (%)	MRI *n* (%)	Liver biopsy *n* (%)	Immunohistochemistry (IHC) (*n*)	Microscopic appearance
Tsou, 2006[27]	Solitary (6) Multiple (2)	7 (87.5) Contrasted: Enhancement on the arterial phase Progressive peripheral enhancement on the portal venous and delayed phase	8 (100) Hypoechoic	2 (25)	6 (75)	NR	Aggregation of neutrophiles
Xiao, 2013[28]	Solitary (7) Multiple (2)	9 (100) Precontrasted: Homogeneous lesions with well-defined margins Contrasted: Mild, irregular peripheral enhancement on the arterial phase Heterogeneous enhancement on the portal venous phase Enhancement on the delayed phase Necrosis accompanying haemorrhage	NR	3 (33.3) Inhomogeneous hypointense on T1WI Inhomogeneous hyperintense on T2WI	2 (22.2)	Vimentin+ SMA+ CD 68+ most cases	Fibroblastic proliferation with infiltration of lymphocytes, plasma cells, and eosinophils Ovoid, medium-sized tumour nuclei with smooth nuclear membranes
Liang, 2014[29]	Solitary (22) Multiple (2)	20 (83.3) Precontrasted: Hypodense lesions Contrasted: Ring enhancement on the portal venous and delayed phases OR No obvious enhancement	24 (100) Hypoechoic	6 (25) Hypointense on T1WI Inhomogeneous hyperintense on T2WI	9 (37.5)	Vimentin+ (8) SMA+ (8)	Fibroblastic proliferation with infiltration of various inflammatory cells and histiocytes
Nigam, 2019[30]	Solitary (14) Multiple (3)	15 (88.2) Precontrasted: Hypodense lesions Contrasted: Peripheral rim enhancement on the arterial phase	17 (100) Hypoechogenic	6 (35.3) Hypointense on T1WI Hyperintense on T2WI	13 (76.5)	NR	Spindle cells in a dense collagenous background with infiltration of plasma cells and eosinophils Clusters of xanthomatous cells with epithelioid cell granulomas, multinucleated giant cells
Ijuin, 1997[31]	Solitary (8)	NR	NR	8 (100) Hypointense on T1WI Hyperintense on T2WI	7 (87.5)	Vimentin+ (8) SMA+ (8) IgG4+ (2)	Collagen fibers in replacement of exfoliated liver cells with infiltration of plasma cells
Horiuchi, 1990[32]	Solitary (7) Multiple (1)	8 (100) Precontrasted: Irregular or lobulated hypodense lesions	8 (100) Mixed echogenicity	NR	2 (25)	NR	Hyalinized collagenosis in bundles or whorls with infiltration of inflammatory cells Xanthogranuloma with proliferation of foamy histiocytes

Supplementary Table III: Continued

First author, year	Imaging features				Histopathological characteristics		
	Solitary / Multiple (*n*)	CT *n* (%)	US *n* (%)	MRI *n* (%)	Liver biopsy *n* (%)	Immunohistochemistry (IHC) (*n*)	Microscopic appearance
Yoon, 1999[12]	Solitary (8) Multiple (2)	10 (100) Precontrasted: Poorly defined hypodense lesions Contrasted: Multiseptate appearance with hyperdense internal septa and periphery	NR	NR	NR	NR	Fibroblastic proliferation with infiltration of foamy histiocytes, plasma cells, and lymphocytes
Kang, 2013[33]	Solitary (7) Multiple (6)	6 (46.2) FDG-PET/ CT: FDG avid with necrosis	NR	13 (100) Target-like hyper- vascular mass Hypointense, hyperintense, or isointense on T1WI Central hyperintense on T2WI with diffusion restriction	11 (84.6)	NR	Fibroblastic proliferation with infiltration of lymphocytes and plasma cells
Ahn, 2011[34]	Solitary (17) Multiple (5)	22 (100) Precontrasted: Poorly defined hypodense lesions Contrasted: Periphery enhancement on the delayed phase	NR	NR	16 (72.7)	IgG4+ (4)	Fibroblastic proliferation with infiltration of histocytes, lymphocytes, multinucleated giant cells, and neutrophiles
Park, 2014[35]	Solitary (38) Multiple (7)	45 (100) Precontrasted: Poorly defined hypodense lesions Contrasted: Peripheral enhancement on the arterial phase Hyperdense lesions with internal hypodense area on equilibrium phase	NR	23 (51.1) Hypointense on T1WI Homogenous hyperintense on T2WI Peripheral rim enhancement at arterial phase on Gadolinium-enhanced images	36 (80)	NR	Infiltration of plasma cells, lymphocytes, neutrophils, and eosinophils
Oh, 2021[13]	Solitary (6) Multiple (1)	7 (100)	NR	NR	2 (28.6)	NR	NR
Koea, 2003[36]	Solitary (3) Multiple (2)	5 (100) Precontrasted: Hypodense lesions with poorly defined margins	4 (80)	NR	4 (80)	NR	Fibroblastic proliferation with infiltration of eosinophils and neutrophils
Milias, 2009[37]	Solitary (4)	4 (100)	3 (75) Cystic lesion	NR	4 (100)	NR	Densely collagenous bundles traverse with infiltration of plasma cells
Stoll, 2010[38]	Solitary (9)	NR	NR	NR	9 (100)	SMA+ (9) ALK+ (8)	Fibroblastic proliferation with infiltration of inflammatory cells Uniform and bland tumour cells with plump, ovoid or bipolar nuclei and vesicular chromatin
Arora, 2021[39]	Solitary (19) Multiple (11)	Precontrasted: Poorly defined or lobulated hypodense lesions FDG-PET/ CT [1 (3.3)]: FDG avid	Hypoechogenic	Heterogeneously enhancing mass Hyperintense on T2WI	26 (86.7)	IgG4+ (5)	Infiltration of lymphocytes and plasma cells Storiform type fibrosis Atypia in the spindle cell component

NR – Not reported,
T1WI – Unenhanced T1-weighted images,
T2WI – T2-weighted images,
SMA – Smooth muscle actin

Supplementary Table IV: Risk of bias and quality evaluation of the included studies assessed by the Newcastle-Ottawa Scale or scale proposed by Murad et al.

Author, year	First Risk of bias
Calomeni, 2013[17]	High quality 6*
Li,1989[22]	Low quality 3*
Qiu, 2013[23]	Medium quality 6*
Yang, 2014[24]	High quality 9**
Tang, 2010[25]	Medium quality 6**
Yang, 2015[11]	High quality 7*
Gao, 2023[26]	Medium quality 5*
Tsou, 2006[27]	High quality 7*
Xiao, 2013[28]	High quality 6*
Liang, 2014[29]	High quality 6*
Nigam, 2019[30]	High quality 6*
Ijuin, 1997[31]	High quality 6*
Horiuchi, 1990[32]	High quality 7*
Yoon, 1999[12]	High quality 6*
Kang, 2013[33]	High quality 7*
Ahn, 2011[34]	High quality 7*
Park, 2014[35]	High quality 7*
Oh, 2021[13]	Medium quality 5*
Koea, 2003[36]	High quality 6*
Milias, 2009[37]	Medium quality 5*
Stoll, 2010[38]	Low quality 4*
Arora, 2021[39]	High quality 6*

* Case series, ** Cohort or comparative studies
Studies scoring between 6-10 were considered 'high quality', scores between 4 and 6 were of 'moderate quality', and scores < 4 were deemed 'low quality'.

Supplementary Table V: Pre-treatment misdiagnosis reported in the included studies

First author, year	Misdiagnosis (*n*)
Calomeni, 2013[17]	Hepatocellular carcinoma (1) Lymphoproliferative disease and abscess (1) Metastatic cancer (1)
Li,1989[22]	Hepatocellular carcinoma (4)
Qiu, 2013[23]	Misdiagnosis (8)
Yang, 2014[24]	NR
Tang, 2010[25]	Unclassified suspicion of malignancy (39)
Yang, 2015[11]	NR
Gao, 2023[26]	Liver cancer (4) Other benign disease (4) Intrahepatic cholangiocarcinoma (1) Metastatic cancer (1) Liver abscess (1) Postoperative recurrence of liver cancer (1)
Tsou, 2006[27]	Hepatocellular carcinoma (3)* Liver abscess (2) Metastatic cancer (1)
Xiao, 2013[28]	Haemangioma (2) Focal nodular hyperplasia (2) Intrahepatic cholangiocarcinoma (2)
Liang, 2014[29]	Hepatocellular carcinoma (10) Metastatic cancer (7) Liver abscess (3) Intrahepatic cholangiocarcinoma (2)
Nigam, 2019[30]	Hepatocellular carcinoma (7) Infectious etiologies (4) Metastatic cancer (2) Intrahepatic cholangiocarcinoma (2) Granulomas (2) Lymphoma (1) Focal nodular hyperplasia (1) Liver abscess (1) Portal cavernoma (1)
Ijuin, 1997[31]	Suspected hepatocellular carcinoma (1)
Horiuchi, 1990[32]	Hepatocellular carcinoma (6)
Yoon, 1999[12]	NR
Kang, 2013[33]	Liver abscess (1)
Ahn, 2011[34]	Unclassified suspicion of malignancy (6) Liver abscess (4)
Park, 2014[35]	Intrahepatic cholangiocarcinoma or hepatocellular carcinoma (23) Liver abscess (8) Lymphoma (2) Liver abscess versus malignancy (1)
Oh, 2021[13]	The majority of liver masses were diagnosed with hepatocellular carcinoma
Koea, 2003[36]	Unclassified suspicion of malignancy (2)*
Milias, 2009[37]	Liver abscess (2) Intrahepatic cholangiocarcinoma (2)
Stoll, 2010[38]	Metastatic cancer (1)
Arora, 2021[39]	Metastatic cancer (11) Liver abscess (7)

NR – Not reported, * Misdiagnosis not resulted from the imaging diagnosis

Supplementary Table VI: Summary of features of IMT on extrahepatic sites

First author, year	Location	Patients(*n*)	Gender of patients (*n*) (male:female)	Mean age (± SD)	Clinical presentation (*n*)	Histological features	Immunohistochemical features (*n*)	Treatment	
								Medical / Rescue surgery (*n*)	Surgical (*n*)
Teoh, 2014[42]	Urinary bladder	182	Male: 88 Female: 94 1:1.1	38.9 ± 16.6 p	Hematuria (69) Dysuria (19) Urinary frequency (18) Lower abdominal pain (13) Loin pain (2)	Spindle cell proliferation with infiltration of plasma cells, lymphocytes, eosinophils, and neutrophils Presence of pleomorphism and necrosis	SMA+: 82 ALK+: 78 Vimentin+: 58 Desmin+: 55	NR	119
Desai, 2014[43]	Skull base	87	Male: 53 Female: 34 1.6:1	46.7 (4–81)*p	Headache (39) Diplopia (29) Vision loss (22) Facial pain (20) Ptosis (17) Proptosis (12) Hearing loss (11) Facial numbness (11) Otalgia (9)	Fibrosis with infiltration of lymphocytes and plasma cells	IgG4+: 11	Steroids 68/6 Antibiotics 1/1 Antibiotics and steroids 3/2	20
Mishra, 2021[44]	Nasopharynx	36	Male: 22 Female: 14 1.6:1	52.2 ± 15.1	Facial pain or headache (36) Cranial nerve (CN) palsies (21) Facial numbness (10)	NR	NR	Steroids 28/0 Antibiotics and steroids 5/1	1
Huang, 2022[45]	Lower cranial nerve	11	Male: 8 Female: 3 2.7:1	51.3 ± 13.0	Dysphagia (7) Hoarseness (5) Tongue atrophy (5)	Fibrosis with infiltration of inflammatory cells	NR	Steroids 5/4	4
Mandato, 2017[46]	Uterus	72	Male: 0 Female: 72 0:72	40.6 ± 14.9 p	Abdominal/pelvic pain / discomfort (15) Vaginal bleeding (13) Fever/weight loss (5) Urinary disorders (2) Fatigue for (2) Uterine prolapse (1)	NR	ALK+: 58 Desmin+ :48 SMA+:43 Vimentin+: 5 CD68+: 4	NR	40
Makhlouf, 2002[47]	Gastrointestinal tract	38	Male: 20 Female: 18 1.1:1	41 ± 23 p	Pain (14) Fever (7) GI bleeding (6) Obstruction (6) Intussusception (4)	Spindle cell proliferation in a collagenous or fibromyxoid stroma with infiltration of plasma cells, lymphocytes, eosinophils, and histocytes	SMA+: 30 Vimentin+: 27 CD68+: 20 Desmin+ :2	NR	34
Neronov, 2020[48]	Jaw-bone	25	Male: 12 Female: 13 1:1.1	34.8 ± 19.6 p	Bone destruction: (25) Soft tissue swelling (14) Ulcerated mucosa (4) Pain (8) Root resorption (7)	Spindle cell proliferation and infiltration of lymphocytes, plasma cells, neutrophils, and eosinophils	SMA+: 16 ALK+: 6 Vimentin+: 8 CD68+: 3 Desmin+: 1	Steroids 3/2	25
Masciocchi, 2011[49]	Limbs (soft tissue)	7	Male: 6 Female: 1 6:1	57 (28–81)*	NR	NR	SMA+: 7	NR	6

NR – Not reported,
* Mean (range),
p – Pediatrics included