Review

Gastrointestinal and hepatic involvement in paediatric systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a multisystemic, autoimmune, inflammatory disease. Gastrointestinal (GI) involvement, extensively described in adults, is less characterised in paediatric-onset SLE (pSLE). The aim of the present narrative review was to provide a comprehensive summary and update on GI involvement in pSLE.

A literature search on PubMed and EMBASE was conducted to identify original articles, reviews, case series and editorials published in English from 2000 to 31 August 2020. Based on this, we reported the prevalence, pathogenetic mechanisms, clinical issues, diagnostic tools and management of each form of GI involvement in pSLE.

Lupus enteritis is the most frequent type of GI involvement in pSLE, followed by intestinal pseudo-obstruction, protein-losing enteropathy, hepatic disease and acute pancreatitis. The most common presenting GI symptoms are non-specific and include abdominal pain, anorexia, nausea, vomiting. In most cases, they are associated with other clinical and laboratory manifestations of SLE. The complications of GI involvement, including perforation and intestinal infarction, can be life-threatening. Laboratory findings and imaging studies can help to rule out non-SLE related causes for GI manifestations and to reveal typical features of the single forms of GI involvement. Early diagnosis and treatment are crucial to improve prognosis and avoid unnecessary surgery. Most SLE GI manifestations respond well to glucocorticoids and immunosuppressants.

In conclusion, GI involvement is frequent in pSLE and its diagnosis and management can be a challenge for clinicians. In view of the limited available data, further studies are needed to better explore the prevalence, prognosis and treatment recommendations for GI involvement in pSLE.

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic, autoimmune, inflammatory disease. Paediatric-onset SLE (pSLE), defined as SLE diagnosed under 16 years of age, accounts for up to 20% cases (1, 2). Its peak age of onset is 12.6 years and the disease is more common in females and in non-Caucasian individuals (2). Although pSLE and adult SLE share some common findings, disease course and prognosis may differ. Children have a severe and systemic presentation at diagnosis more frequently, requiring prompt hospitalisation in approximately 40% of patients (3-5). Compared to adulthood, renal, neurological, and haematological involvement are frequent (1, 2). Atypical clinical presentations with rare manifestations, typically onset under 6 years of age, can delay diagnosis (1).

Gastrointestinal (GI) manifestations of SLE are well known and described in adults (6, 7), while paediatric data are limited (8). The aim of the present narrative review was to provide a comprehensive summary and update regarding the GI involvement spectrum in pSLE, focusing on prevalence, pathogenetic mechanisms, clinical issues, diagnostic tools and management.

Methods

An extensive literature search was carried out by two reviewers (ST, CR), independently. We used PubMed and EMBASE to identify original articles, reviews, case series and editorials published in English from 2000 until 31 August 2020. The keywords included: systemic lupus erythematosus, lupus, SLE, gastrointestinal, abdominal, lupus

Table I. Summary of clinical data on available pSLE cohorts focusing on GI involvement.

Author	Number of cases	Median age (range)	Cases with GI involvement (%)	Cases with GI involvement at disease onset (%)	Initial symptom/finding n (%)		Causes of GI involvement n (%)	
Richer *et al*. [9]	201	11.3 (4.5-16)	39 (19%)	32 (15.9%)	Abdominal pain Vomiting Diarrhoea	34 (87%) 11 (28%) 11 (28%)	AP Surgical abdomen	11 (28%) 5 (12%)
Sönmez *et al*. [8]	69	13 (5-17)	19 (27.5%)	13 (18.8%)	High transaminases Hepatomegaly Jaundice Abdominal pain	11 (57.9%) 5 (26.3%) 4 (21.1%) 3 (15.8%)	AIH LE	8 (42.1%) 1 (5.2%)
Tu *et al*. [14]	258	14.7 (7.3-18)	23 (8.9%)	NA	Abdominal pain	23 (100%)	LE Appendicitis AP IPO	12 (31.6%) 4 (10.6) 5 (13.2%) 2 (5.35)

AIH: autoimmune hepatitis; AP: acute pancreatitis; GI: gastrointestinal; IPO: intestinal pseudo-obstruction; LE: lupus enteritis; pSLE: paediatric-onset systemic lupus erythematosus; NA: not available.

mesenteric vasculitis, lupus enteritis, intestinal pseudo-obstruction, intestinal pseudo-obstruction, protein-losing enteropathy, protein-losing gastroenteropathy, lupus hepatitis, autoimmune hepatitis, pancreatitis, child, paediatric, paediatric and juvenile. We also searched the references of identified articles for further related papers.

Prevalence and features of GI involvement

Since limited number of studies, mostly case reports, report GI involvement in pSLE, we identified the 3 largest paediatric cohorts regarding this topic; the features of GI involvement of these cohorts are summarised in Table I.

The incidence of GI involvement in different ethnic groups was described only by Richer *et al*. (9): in their French paediatric cohort, the proportions of black and north African children with GI involvement were 34% and 17%, respectively. The reported prevalence of GI involvement in pSLE ranges from 17 to 27.5% (5, 8, 9). At disease diagnosis, GI involvement has been described in 15.9% pSLE cases (32/201) by Richer *et al*. (9) and in 18.8% (13/69) by Sönmez *et al*. (8). GI manifestations rarely occur as the single presenting feature of pSLE, since additional other clinical features are often present at the disease onset (9). However, few reports described the abdominal involvement as the sole presenting feature of pSLE (10-13).

Lupus enteritis (LE) is the most frequent type of GI involvement in SLE, either in adults and in children, followed by intestinal pseudo-obstruction (IPO), protein-losing enteropathy (PLE), hepatic disease, and acute pancreatitis (AP), respectively. Regardless of the underlying cause, abdominal pain is the main GI symptom, followed by nausea, vomiting, and rarely, rectal bleeding (5, 9). The frequency of the different forms of GI involvement ranges according the available paediatric studies. According to Tu *et al*., the main cause of abdominal pain in children is LE, whereas hepatic disease, peptic ulcer and malignancy account for abdominal pain preferably in adults (14). In the paediatric cohort reported by Bader-Meunier *et al*., AP was the most common cause of abdominal pain (5). Conversely, autoimmune hepatitis was the principal GI manifestation related to pSLE in the cohort described by Sönmez *et al*. (8). Eventually, abdominal manifestations in pSLE may be not specifically due to the disease, but rather to a co-morbidity situation (such as pneumonia), therefore distinguishing SLE-related and non SLE-related causes of abdominal manifestations can result challenging.

Lupus enteritis

LE, also known as lupus mesenteric vasculitis, is one of the most common manifestations of GI involvement in SLE (7). It can be defined as vasculitis or inflammation of the small bowel, with supportive image and/or biopsy findings (15). Globally, the estimated prevalence of LE ranges between 0.2% and 14% among all SLE patients (16) and accounts for 29–65% cases of acute abdominal pain (17). LE is one of the main manifestations of GI involvement and the most common cause of abdominal pain also in pSLE. It was significantly more prevalent in pSLE patients (31.9%) when compared to the adult SLE group (13.9%) (14). However, it is exceedingly rare that LE represents the sole initial presentation of pSLE (11). In contrast, in the retrospective study by Sönmez *et al*., LE was demonstrated only in one child out of 19 pSLE patients with GI manifestations (8). Most studies demonstrated that LE occurs with evidence of active disease in adults, assessed by SLE disease activity index (SLEDAI) score (16, 18, 19), whereas literature shows conflicting results regarding this association in children (9, 13, 14, 20). Tu *et al*. also reported that children were more likely to experience recurrent episodes of LE if compared to adults (39.1% *vs*. 14.8%) (14).

The underlying aetiology for the enteric vasculitis may be due to different pathogenetic mechanisms. LE can be due to leukocytoclastic vasculitis secondary to immune complex deposition in vascular walls or to thrombosis of the intestinal vessels, and it is possibly related to circulating antiphospholipid antibodies (17).

Due to the frequent involvement of the superior mesenteric artery, the ileum and jejunum are the most frequently affected sites (8–85% cases) (20-22). Multifocal bowel segmental involve-

ment is commonly encountered (21). The rectum is involved in about 14% cases, while gastric involvement is extremely rare (20).

Signs and symptoms of LE can range from mild, non-specific abdominal pain, accompanied by nausea, vomiting and diarrhoea, to acute abdomen with sudden onset or even to severe GI bleeding (18, 23). Although uncommon, LE can also result in bowel ischaemia and intestinal necrosis. Subsequently, when unrecognised, it can lead to perforation and haemorrhage with significant mortality rates, up to 50% (11, 20).

Imaging studies may provide some diagnostic clues to LE. Plain abdominal radiographs are generally normal or non-specific in the early stages; while in advanced stages they may show intraperitoneal free air, pneumatosis intestinalis, ileus or pseudo-obstruction (18). Abdominal ultrasound seems to be a useful tool to confirm bowel oedema or ascites. It is thus helpful to support prompt clinical diagnosis, as well as, in follow-up, to confirm the clinical recovery (23). Abdominal contrast-enhanced computed tomography (CT) is the gold standard tool to diagnose LE, demonstrating multiple segments of focal bowel wall thickening, diffuse bowel wall enhancement with peripheral rim enhancement (target sign), segmental intestinal dilatation, engorgement of the mesenteric vessels (comb sign), blurred mesenteric fat and ascites (24, 25). Although its use has rarely been reported in children (26), CT angiography should be considered as a noninvasive technique able to identify vasculitic alterations of mesenteric vessels. Like CT scan, magnetic resonance (MR) enterography can reveal signs of bowel ischaemia due to GI vasculitis (27). In view of the absence of radiation exposure, it could be implemented in pSLE for LE diagnosis and follow-up. This imaging modality could allow the detection of some findings usually associated with LE, such as a wall thickening of the last ileal loop, with a concomitant indentation of the mucosal and serosal sides, referable to oedema and/or haemorrhage of the submucosal layer, and the fluid collection within the abdominal cavity. However, at the moment data on MR enterography findings in LE are limited (28) and further studies are needed to validate its use both in adult and paediatric settings.

Endoscopy and histopathology, rarely useful to diagnose LE, can support the diagnosis in subjects with atypical features of LE or to rule out mimicking conditions (11, 23). Macroscopic aspects of LE range from segmental oedema to discrete ulceration, gangrene and perforation (17). Histologic samples generally give scarce diagnostic information because only superficial tissue is collected; histologic alterations include small-vessel arteritis and venulitis. Immunohistochemistry can demonstrate immune complex, C_3, and fibrinogen deposition, with the final outcome of necrosis, inflammatory cell infiltration and thrombosis of the affected vessels (17, 26).

No randomised trials investigating treatment and outcome in LE are available. Currently, bowel rest, intravenous fluids, glucocorticoids and, in severe cases, immunosuppressants represent the main stand therapeutic approaches (13, 26, 29). Intravenous glucocorticoids are the first choice, most commonly methylprednisolone 1–2 mg/kg/day followed by oral prednisone or, alternatively, pulse methylprednisolone of up to 1 g/day for 3–5 days (26). An immunosuppressant is added in patients with concomitant vital organ involvement, and cyclophosphamide, mycophenolate mofetil or azathioprine are the most used agents (11, 26). Rituximab has also been successfully described in case series (26). For patients with possible intestinal necrosis or perforation, laparoscopy or laparotomy should be promptly performed. The importance of early laparotomy was emphasised by the study of Medina *et al*., that demonstrated significantly higher survival in adult patients who underwent early intervention: no death was found when laparotomy was undertaken within 24–48 hours *versus* 10 out of 11 when it was performed after 48 hours. Therefore, the authors recommend early surgery in all SLE patients with established acute abdomen, refractory to medical treatment (19).

Intestinal pseudo-obstruction

IPO, defined as ineffective propulsion in the intestinal tract, should be considered in the presence of clinical features of intestinal obstruction without a detectable organic causative lesion (30). Recently, it has been recognised as an uncommon but severe complication of pSLE: in the French multicenter study by Bader-Meunier *et al*., IPO was found in 2 out of 26 patients with abdominal manifestations (5). Scattered paediatric case reports described IPO also as the presenting feature of the disease (31, 32). Yamazaki-Nakashimada *et al*. described 2 children manifesting IPO caused by eosinophilic enteritis as the presentation of pSLE (33). This manifestation generally occurs in the setting of active disease, but it can also occur with low SLEDAI score (21).

The pathogenic mechanism of this complication seems to be heterogeneous. IPO likely reflects a dysfunction of the visceral smooth muscle and/or of the enteric nervous system, which may or may not be secondary to a vasculitic process (30). This aetiology is further confirmed by the frequent association of IPO with uretero-hydronephrosis (66.7% in the review of 18 adult patients by Mok *et al*.) (30) and interstitial cystitis, which has been reported also in paediatric reports (31, 33).

IPO involves small bowel more frequently than large bowel (34). The clinical presentation usually includes subacute abdominal pain together with nausea, vomiting and constipation or diarrhoea, as well as a distended, tender abdomen with hypoactive or absent bowel sounds (30, 33). Weight loss can also occur when IPO is a chronic condition. Of note, data on adults reveal that only one third of patients with urinary tract involvement have urinary symptoms (21, 29).

The diagnosis of IPO requires abdominal imaging. Plain abdominal radiographs can reveal dilated small and large bowel loops with multiple air-fluid levels and thickened intestinal wall. Abdominal CT can show mild ascites and rule out mechanical obstruction (6, 18).

pSLE patients with IPO and/or uretero-hydronephrosis must be considered as

having active SLE independently of the disease activity scoring and require early aggressive treatment with high-dose glucocorticoids with or without other immunosuppressants, as well as broad spectrum antibiotics, promotility drugs such as octreotide, and bowel rest (21). The most used immunosuppressants are azathioprine, cyclophosphamide and cyclosporine A (18). Delay in diagnosis may result in life-threatening complications such as bowel necrosis or perforation, and acute renal failure (21). A high level of awareness of this complication is needed to avoid unnecessary surgery.

Protein-losing enteropathy

PLE is a condition characterised by hypoalbuminaemia secondary to loss of serum protein from the GI tract (7). It appears to be more frequent in Asiatic population. Reported prevalence ranges between 3.2 and 7.5% SLE patients in Chinese population (35, 36). Only 11 pSLE patients with PLE have been reported in literature (37, 38). Several pathogenetic mechanisms have been proposed for PLE in SLE: increased GI vessel permeability due to vasculitis, complement conversion leading to vasodilatation and cytokine-mediated damage, and GI lymphangiectasia (7); such different mechanisms could also coexist. PLE can be present either at onset or during the course of the disease. The systematic review by Al-Mogairen *et al*. focusing on all SLE patients demonstrated that peripheral oedema was the most common clinical presentation (80%) of PLE, followed by ascites (48%) and diarrhoea (48%) (39). Hypoalbuminaemia is the typical laboratory finding, not associated with proteinuria, hepatic disfunction or malabsorption (6). Increased fecal clearance of α-1 anti-trypsin suggests the presence of PLE. Technetium-99m labelled albumin scintigraphy is the best diagnostic exam for PLE as it also indicates the GI site of protein leakage; however, this exam is rarely performed in paediatric age (18). The most common site of protein leakage is the small intestine (6). GI ultrasound, CT, endoscopy can show bowel oedema, ascites or non-specific inflammation. Histology can be normal or show non-specific inflammatory changes (18).

Most of the reported PLE cases are responsive to high-dose glucocorticoids. In steroid-refractory cases, an immunosuppressant is generally added, mainly azathioprine or cyclophosphamide (18, 37). Sansinanea *et al*. reported a paediatric case whose PLE was refractory to steroids and to different lines of immunosuppressants; the patient had a good and sustained response with rituximab (40). PLE supplemental therapies include albumin infusion and diuretics. In addition, octreotide has been recently reported as able to reduce intestinal microvascular blood flow, decrease local lymph formation, and ameliorate lymphatic dilation (39).

Hepatic involvement

Liver involvement is not part of SLE diagnostic criteria; however, altered liver function tests (LFTs) are seen in up to 60% of all SLE patients (41, 42). A wide spectrum of hepatic disorders has been associated with SLE. The most common causes of altered LFTs are hepatotoxic drugs (especially methotrexate, non-steroidal anti-inflammatory drugs, azathioprine and cyclophosphamide) and concurrent viral hepatitis (43, 44). On the other hand, a true autoimmune liver involvement can occur during the disease course: it has been described with variable frequencies and has not been fully characterised. Current evidences suggest that autoimmune liver involvement can be distinguished in two forms: lupus hepatitis (LH) and autoimmune hepatitis (AIH). LH is defined as a parenchymal injury associated with SLE (45). AIH is a progressive, chronic inflammatory disease, diagnosed in accordance with generally accepted diagnostic criteria (46): elevated LFTs, hypergammaglobulinaemia, presence of autoantibodies (anti-nuclear, anti-smooth-muscle or anti-liver-kidney microsomial) and interface hepatitis with lymphocytic infiltrates in liver biopsies.

The epidemiology of autoimmune liver involvement in pSLE has been described in scattered studies and single reports (47-49). In the British study by Irving *et al*. comparing autoimmune liver disease in adults and children, the prevalence in pSLE was 9.8%, significantly higher than 1.3% in adults. All paediatric patients had biopsy-proven AIH and developed AIH prior to SLE (50). Deen *et al*. found a lower prevalence of AIH (1.8%) in pSLE population (51). A large Brazilian multicentre study on 847 pSLE patients demonstrated a very small prevalence (0.8%) of AIH, confirmed by laboratory and histologic findings; in these patients, hepatomegaly was the distinctive feature, AIH manifested during adolescence, in the first years after SLE onset and was associated with mild liver and SLE disease manifestations (52). The reported prevalence of LH in adults ranges between 3 and 24.5%, while prevalence in pSLE has not been fully established (44, 53).

Clinical and biochemical features of AIH and LH overlap in most cases. Clinical presentation is generally mild and subacute, including hepatomegaly and, more rarely, jaundice and splenomegaly (44). The most common laboratory alteration is elevation in transaminase levels (42). As already mentioned, AIH is associated with anti-smooth-muscle or liver-kidney microsomial type-1 antibodies. LH is associated with the presence of anti-ribosomal-P antibodies. Histologic presentation of AIH is as interface hepatitis with lymphocytic infiltrates in liver biopsies; while LH presents with lobular hepatitis, atrophy and necrosis of the central hepatic cells, fatty infiltration, lymphocytic inflammatory infiltrate (41, 54, 55). Zheng *et al*. demonstrated a positive intense deposits of complement 1q in 7 out of 10 adult patients with LH, which were absent in all patients with other liver diseases (53). Therefore, although the boundary between AIH and LH may be unclear because they share similar clinical and biochemical features, the specific autoantibodies and histologic characteristics can help to differentiate them. Compared to LH, untreated AIH leads to a more severe hepatic involvement (41, 43). As regards treatment protocols, standard treatment for AIH is high-dose prednisone, generally associated with immunosuppressants (azathioprine) (43, 46). Although no definite

Table II. Summary of the main characteristics of the different forms of GI involvement in pSLE.

Features	Prevalence	Clinical manifestations	Diagnosis	Treatments
LE	5.4-31.9%	Abdominal pain Nausea Vomiting Diarrhoea Perforation (rare) Haemorrhage (rare)	Contrast-enhanced CT: target sign, combs sign, ascites Other: x-ray, ultrasound, endoscopy	IV glucocorticoids Immunosuppressant if vital organ involved (cyclophosphamide, mycophenolate mofetil, azathioprine) Surgery in case of perforation/haemorrhage
IPO	NA	Subacute abdominal pain Nausea Vomiting Constipation/diarrhoea Weight loss	x-ray CT	IV glucocorticoids Immunosuppressant in selected cases (azathioprine, cyclophosphamide, cyclosporine A)
PLE	NA	Peripheral oedema Ascites Diarrhoea	α-1 anti-trypsin increased fecal clearance Technetium-99m labelled albumin scintigraphy Other: ultrasound, CT, endoscopy	IV glucocorticoids Immunosuppressant in refractory cases (azathioprine, cyclophosphamide)
AIH	0.8-9.8%	Hepatomegaly Jaundice Splenomegaly	Anti-SM or anti-LKM-1 antibodies Biopsy: interface hepatitis with lymphocytic infiltrates	Oral glucocorticoids Immunosuppressant (azathioprine)
LH	NA	Hepatomegaly Jaundice Splenomegaly	Anti-ribosomal-P antibodies Biopsy: lobular hepatitis, atrophy and necrosis of the central hepatic cells, fatty infiltration, lymphocytic inflammatory infiltrate	Oral glucocorticoids Immunosuppressant in selected cases
AP	2.6-6%	Abdominal pain Vomiting	Ultrasound CT	IV glucocorticoids Immunosuppressant in selected cases

AIH: autoimmune hepatitis; AP: acute pancreatitis; CT: computed tomography; IPO: intestinal pseudo-obstruction; IV: intravenous; LE: lupus enteritis; LH: lupus hepatitis; NA: not available; PLE: protein-losing enteropathy; pSLE: paediatric-onset systemic lupus erythematosus; SM: smooth-muscle; LKM-1: liver-kidney microsomial-1.

guidelines exist for LH, it generally responds well to moderate to high doses of prednisone without progression to end-stage liver disease, although adding an immunosuppressant agent can be necessary in some cases (44, 56). Therefore, in children with pSLE and altered LFTs, firstly drug toxicity and infections need to be ruled out. Subsequently, autoantibody screening and, if necessary, liver biopsy should be performed to establish the differential diagnosis between LH and AIH. The prompt diagnosis and treatment adjustment can improve disease outcomes and prevent liver disease progression (43). Of note, Fallahzadeh *et al*. described the unique case of a 6-month-old infant presenting with unexplained hepatosplenomegaly and non-necrotising granulomatous liver involvement, who later developed other disease manifestations, finally diagnosed with pSLE at the age of three years (57).

Acute pancreatitis

AP is a rare but potentially life-threatening manifestation of SLE (58). AP is diagnosed by the presence of at least two of the three following features: abdominal pain or vomiting, increased serum levels of pancreatic amylase and/or lipase (at least 3 times greater than the upper limit of normal), and consistent imaging findings on abdominal ultrasound or CT (59, 60). Reported prevalence of AP in pSLE ranges between 2.6% and 6% (9, 21, 60-62). In the cohort described by Bader-Meunier *et al*., AP was the most common cause of abdominal pain (5). Wang *et al*. compared AP in the setting of pSLE and adult SLE: children had significantly higher prevalence, complications, severe forms, concurrent SLE symptoms, disease activity and mortality (53.8% *vs*. 14.8%) than adults (63). AP generally occurs in the first 2-5 years of SLE diagnosis and is associated with high SLEDAI score at its diagnosis (60, 64). Pathogenesis is complex and multifactorial, not yet fully understood: immune complex deposition, microthrombi, vasculitis, intimal thickening, and ischaemia have all been studied as involved mechanisms (21, 63). Of note, SLE patients can develop AP due to other causes, such as mechanical obstructions (including cholelithiasis), toxics or medications (alcohol, azathioprine), hypertriglyceridaemia and hypocalcaemia, as well as viral infections or sepsis. Therefore, the diagnosis of SLE-related AP can be confirmed if the other possible causes are excluded (64).

The clinical and laboratory presentation of AP is similar to non-SLE patients, except for the association with other clinical or laboratory findings due to SLE disease. Ultrasound and CT can detect pancreatic oedema, necrosis, haemorrhage, peripancreatic inflammation, acute fluid collections, pancreatic abscess or pseudocyst (21). Apart from supportive care, intravenous glucocorticoids are generally effective; other treatment options include immunosuppressant (cyclophosphamide) or plasmapheresis (21).

Several studies showed an association between AP and macrophage activation syndrome (MAS) in pSLE (61-65). MAS is a severe, potentially life-threatening complication of paediatric systemic inflammatory disorders, espe-

cially rheumatic diseases. The common clinical and laboratory features used to establish MAS diagnosis include non-remitting fever, cytopenia, hepatomegaly, splenomegaly, coagulopathy with hypofibrinogenaemia, hypertriglyceridaemia and hyperferritinaemia. MAS, mainly described in association with systemic juvenile idiopathic arthritis (sJIA) with a frequency reported as 7–13%, has been increasingly recognised also in pSLE (61, 62, 65-67). According to available data comparing MAS in pSLE and in sJIA, this complication occurs more frequently at disease onset of sJIA (67) and generally does not recur in pSLE patients (68). In addition, patients with MAS and pSLE compared to those with sJIA, are older, received more mechanical ventilation and cardiovascular support, seem to have more frequently central nervous system involvement (66) and fatigue (67); in contrast, cutaneous rash appears less frequently (67). Parodi *et al*. (69) developed preliminary diagnostic guidelines for MAS in pSLE. Subsequent studies showed further evidence for the clinical significance of these guidelines (68, 70). Therefore, the preliminary diagnostic guidelines for MAS have been used in studies focusing on this complication in pSLE and assessing its association with AP. Campos *et al*. showed that 10 out of 11 pSLE patients with AP (90%) fulfilled criteria for MAS (61). Gormezano *et al*. compared AP and MAS concurrence in adults and children with SLE: MAS criteria were more frequently fulfilled in pSLE patients than in adults with SLE and AP (85% *vs*. 30%). On the other hand, AP occurred more frequently in patients with MAS than in those without MAS, both in children and adults (62). Lin *et al*. reported 87 pSLE cases with AP after literature review of the last 30 years: 52.86% of them had MAS at the same time (65); this frequency is much higher than those without pancreatitis, which is reported ranging from 9% (68) to 20% (71). These findings suggest the hypothesis that pancreas could be a target organ of MAS. The pathogenetic mechanism responsible for MAS during AP is not completely clear. However, it has been hypothesised that during AP there are mediators released by the damaged pancreas able to activate macrophages. When activated, these inflammatory cells could act to amplify the inflammatory response triggered in the pancreas through the generation of more cytokines and inflammatory mediators in systemic organs (72).

Conclusion

The aim of the present narrative review was to analyse the characteristics of GI involvement in pSLE. The main features of the described forms are summarised in Table II.

Although not included in diagnostic criteria, GI involvement can be frequent in pSLE and can also be the presenting feature, representing a diagnostic challenge for clinicians. The most common presenting symptoms are non-specific and include abdominal pain, anorexia, nausea, vomiting. In most cases, they are associated with high disease activity and therefore with other clinical and laboratory manifestations of SLE. The complications of GI involvement, including perforation and intestinal infarction, can be life-threatening.

Laboratory findings and imaging studies can help to rule out non-SLE related causes for GI manifestations and to reveal typical features of LE, IPO, PLE, LH, AIH, and AP. Early diagnosis and adequate treatment are crucial to improve prognosis and avoid unnecessary surgery. Most SLE GI manifestations respond well to glucocorticoids and immunosuppressants.

The main limitation of this review is the available data in pSLE, mainly represented by case report or case series, while extended paediatric cohorts are limited in number. Therefore, further studies are needed to better explore the prevalence, prognosis and treatment recommendations for GI involvement in pSLE.

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