GRZEGORCZYK, Aleksandra, PACHLA, Magdalena and DARDZIŃSKA, Nicol. Chronic intestinal pseudo-obstruction as the same symptom of various basis - review of literature. Journal of Education, Health and Sport. 2024;76:56472. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.76.56472
https://apcz.umk.pl/JEHS/article/view/56472

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 27.11.2024. Revised: 15.12.2024. Accepted: 18.12.2024. Published: 21.12.2024.

Chronic intestinal pseudo-obstruction as the same symptom of various basis - review of literature

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Purpose

The aim of this study is to present the current state of knowledge on the etiology of chronic intestinal pseudo-obstruction.

Review methods

The PubMed and Google Scholar databases were used for the literature review. The following phrases were searched for in English: “chronic intestinal pseudo-obstruction”, “gastrointestinal motility disorders”, “CIPO”.

Abstract

The aim of this work is to discuss the known causes of chronic intestinal pseudo-obstruction. Determining the etiology of the symptoms reported by the patient, such as: abdominal pain, bloating, nausea, constipation, heartburn or regurgitation, the cause of which cannot be clearly identified in imaging tests as mechanical intestinal obstruction, is necessary to implement proper therapy. We distinguished, among others: infections, gene mutations, cancer and paraneoplastic syndromes and autoimmune diseases. This broad range of causes shows the complexity of this disease.

Among pathogens, the most common cause are viruses, especially herpesviruses, what is more bacterial infections and gut dysbiosis must be taken under consideration. We found that specific pathway gene mutations can cause obturation symptoms which need extended diagnostic tests. Paraneoplastic syndromes should be examined as a possible etiological factor while looking for the cause of this disease and anticancer treatment can be either a solution for the chronic intestinal pseudo-obstruction symptoms or a cause of them. Lastly we discussed autoimmune diseases as a part of the inflammation problem of the bowel.

The goal is to emphasize how important it is to draw attention to the need of looking at the patient and his ailments integrally, which will enable an accurate diagnosis to be made and the appropriate treatment to be effectively selected. We found it very important to think unconventionally with every patient we deal with and what can be done thanks to a great amount of knowledge provided by other doctors.

Keywords: chronic intestinal pseudo-obstruction, CIPO, gastrointestinal motility disorders

Introduction

Chronic intestinal pseudo-obstruction (CIPO) is a rare gastrointestinal disorder presented by symptoms suggesting mechanical intestinal obstruction without actual blocking of the intestinal lumen. Such a situation may occur in every segment of the gastrointestinal tract. Despite research effort, many physicians struggle with diagnosing and treating this condition.[1,2] Symptoms of CIPO include abdominal pain, bloating, nausea, constipation, heartburn or regurgitation.[3] The exact number of patients suffering from CIPO is unknown, however researchers studying this condition base their studies on rather small groups, which suggests its rarity.[4] Despite the fact that CIPO is a rare diagnosis a lot of possible factors have been suggested as its causes, including infections, genetic mutation, neoplasms, drugs and gut microbiota. Such extensive etiology means that treatment methods vary from conservative treatment to surgery.[2,4-9]

In cases of patients, who develop specific symptoms, but do not fit into a known pattern, an extended view is necessary. The aim of this review is to conclude present-day knowledge of various etiological factors of CIPO. Such awareness may help to avoid taking unnecessary measures, which can even be harmful to the patient.[10]

Pathogens

The history of microbiology shows that many researchers throughout time linked various diseases with external factors. The discovery of bacteria in 1693 by Anton van Leeuwenhoek and then the germ theory stated in late 1870's by Louis Pasteur and Robert Koch established background for further studies of infectious diseases.[11] As it turns out CIPO can be connected with infectious factors, especially with various viruses and protozoans.[8, 12-15]

First group of viruses with clinical connection to CIPO are well known as herpesviruses. Even though the group consists of many more viruses, to date, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and varicella zoster virus (VZV) have been found as causes of CIPO cases.[13, 16, 17]

There are known clinical cases describing infants with intestinal pseudo-obstruction, where physicians linked its etiology with CMV infection. Both reported patients were about two-months-old, presenting symptoms from gastrointestinal system such as vomiting, diarrhea and dehydration. Both patients underwent barium enema which excluded mechanical obstruction and had laboratory confirmed CMV infection.[8, 12] Nevertheless, elderly patients may present similar symptoms which retreat after antiviral therapy.[18] Another child with CIPO presented with pharyngitis and an acute abdominal ileus, with no signs of obstruction during laparotomy. Postoperatively, he suffered from prolonged intestinal obstruction, pandysautonomia, and encephalomyelitis.[19]

Human polyomavirus, JC virus (JCV) was first discovered in a patient suffering from Hodgkin's lymphoma and progressive multifocal leukoencephalopathy (PML). It is a DNA virus and the primary infection occurs mostly in childhood. Immunodeficient patients can experience reactivation which mostly leads to PML but also implicate colorectal cancer.[20] As it turns out, there are several cases of CIPO, where connection to JCV has been suggested. However, authors point out that CIPO as well as PML may occur mostly among immunodeficient patients.[21, 22]

In opposition to viruses, to date, there are not many articles about CIPO caused by bacteria. There is a clinical case of a patient suffering from lower back-pain radiating to the right lower extremity and lower abdomen, urinary restriction and chronic constipation, non responding to laxatives. After many tests and unsuccessful empiric treatment the diagnosis of chronic Lyme disease was stated. The patient was administered with antibiotic with significant clinical improvement and full recovery in 3 months time.[23]

Protozoans are a known factor for various diseases, some of which present with non obvious symptoms. In literature it has been documented that several species caused CIPO. Two independent clinical cases state that during the diagnostic process of patients with long term pseudo obstruction, stool investigation and antibodies examination may give important information, leading to proper diagnosis and treatment. One team found Strongyloides stercoralis larva and administered ivermectin.[14] Another one found Giardia lamblia

trophozoites, which let them start metronidazole treatment.[15] Both patients reacted well to administered drugs and improved in a short time.

As shown above, CIPO can be related to various infectious factors. However it is known that organ dysfunction can be connected to dysbiosis of human microbiota. Scientists explored the impact of intestinal microbiota on enteric nervous system (ENS) and its connection with CIPO. They proved that mucosa-associated microbiota in pediatric patients diagnosed with CIPO differed from the one present in healthy children's intestines.[2] Another group of scientists conducted an experiment with fecal microbiota transplantation. A group of 9 patients with CIPO took part in that experimental treatment, as a result both symptoms and computer tomography imagining scores of intestinal obstructions were notably reduced.[24]

Gene mutations

CIPO classification is based on the presence of neurogenic or myogenic dysfunction in the intestine, caused by gene mutation.[25] Many different factors, internal and external, contribute to the dysfunction of smooth muscles, enteric nervous system or Cajal cells present in the digestive system. The type of damaged tissue is related to the mutation of individual genes, which to varying degrees contribute to disturbances in its structure, function or further development, leading directly or indirectly to the symptoms of CIPO.[26]

One of the most important is the PTEN gene located on chromosome 10, the proper functioning of which is of great importance for the proper development and functioning of cells of the nervous system. Its mutations are also a field of research for autism spectrum disorders.[27] It is considered as a tumor suppressor gene, and in case of its mutation, cancer processes may be triggered.[28] Enteric nervous system is based on the proper functioning of the PTEN pathway. The cause of CIPO symptoms is the loss of the PTEN gene. Potential treatment for CIPO are drugs that modify the PTEN-dependent transmission pathway, i.e. PI3K/PTEN-AKT-S6K signaling pathway.[9]

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an autosomal recessive disease, caused by a defect in the TP gene, the mutation product of which leads to mitochondrial DNA damage and disorders of its functioning.[29] TP enzyme activity is low, plasma thymidine and deoxyuridine are elevated.[30] The accumulation of abnormal products damages mtDNA, which leads to the symptoms of gastrointestinal dysmotility over the years. This affects the functioning not only of the smooth muscles of the digestive tract, but also of

the vascular muscles.[31] A potential treatment for MNGIE may be hematopoietic stem cell transplantation (HSCT).[32]

The examples presented above show that more and more genes are being discovered whose mutations lead to CIPO symptoms. This emphasizes how extensive diagnostics should be considered in a patient in order to find out the cause of his symptoms and clinical condition. In some cases, it may be necessary to perform a multigene panel.[33]

Cancer

Despite the significant pace of medical development, malignant tumors remain the second most common cause of death, and their percentage is still increasing.[34] The problem is to make the correct diagnosis at the earliest possible stage of the disease, when remission is possible. Most cancers in their early stages do not cause symptoms or they are very mild.[35] The initial manifestation of oncogenesis at various stages of advancement may be a paraneoplastic syndrome, which is caused by changes in the body's immune response and is not the result of the direct action of the tumor.[36] About 8% of patients diagnosed with cancer suffer from paraneoplastic syndrome (PNS).[36] It is the cause of approximately 27% of deaths in oncology patients.[37] It occurs most often in small cell lung cancer (SCLC), breast cancer and gynecology and hematological malignancies.[38] Clinical presentations of PNS include symptoms from different organ systems: neurological, endocrine, rheumatological, hematological ect.[36]

CIPO paraneoplastic syndrome is rare but highly fatal. It is classified as a neurological manifestation and is most often associated with SCLC. Anti-Hu antibodies are positive in paraneoplastic CIPO [39], but it has been proven that these antibodies can also be positive without the presence of cancer.[40] In the case of paraneoplastic CIPO, an attempt to use prokinetic as well as anti-secretory agents does not bring satisfactory results. Treatment of the underlying disease contributes to the reduction of the level of anti-Hu antibodies, without affecting the patient's well-being.[39]

Clinical cases have been described in which the symptoms of CIPO disappeared after the tumor achieved a complete response to chemoradiotherapy. In pursuit of such a goal, it is important to initiate therapy before irreversible changes in neural connections occur, which CIPO can cause as a result of paraneoplastic syndrome. Symptoms of gastrointestinal obstruction may go before the diagnosis of SCLC by approximately 8.7 months [5], and thorough cancer screening should be performed, especially when serological markers such as

ANNA-1, PCA-1, or N-type calcium channel-binding antibodies are positive despite the unknown cause.[41]

In contrast, anticancer therapy may cause CIPO symptoms. Immune checkpoint inhibitors, such as pembrolizumab, often cause immune-related adverse events (irAEs), the frequency of which is estimated at approximately 26.82% in any grade of severity. Their occurrence is not related to the dose of the drug used. Most irAEs that clinically present as gastrointestinal symptoms present as diarrhea. Anti-PD-1/PD-L1 agents are widely used in chemotherapy, e.g. melanoma, non-small cell lung cancer (NSCLC) or renal cell carcinoma (RCC).[42] Symptoms do not differ from CIPO caused by other causes - intestinal obstruction occurs without a mechanical cause. During the therapeutic procedure, the supply of the drug causing symptoms should be discontinued. It is known that the administration of glucocorticoids is not beneficial. The most important thing in the procedure is to provide bowel rest and, if necessary, use gut mobility stimulators. It is important to realize that not all drugs with the same mechanism of action will cause the same side effects. After changing the drug, e.g. from nivolumab to pembrolizumab, side effects may come from different systems, have different severity and do not always have to disqualify the patient from further treatment. If side effects occur, changing one drug to another one from the same therapeutic group may be beneficial, not necessarily to a drug with a different mechanism of action.[43]

Autoimmune diseases

In most cases, the nature of CIPO remains idiopathic. However, it can occur secondary to diseases affecting the motor function of the gastrointestinal tract. It manifests as a secondary cause of gastrointestinal motility disorders, including pathology of the intestinal wall myocytes, as well as the extrinsic and intrinsic neural networks. Treating patients with this diagnosis is usually challenging and long-term treatment outcomes can be dissatisfying.[10] However, the situation is different for patients suffering from systemic lupus erythematosus (SLE), where ureterohydronephrosis, seen in 67% of cases in one series, and histopathological evidence of intestinal leiomyocytes damage are often observed.[44-47] This may suggest that the systemic autoimmune process targets smooth muscle cells.[46]

A clinical case of a woman has been described in the literature. She was diagnosed with SLE hospitalized due to worsening health, experiencing arthralgias, abdominal discomfort, distension, and obstipation. Distended loops of the large and small bowel were detected in the examination, without obvious signs of obstruction. The interesting finding

were the changes in the intestinal wall, which were not typical for lupus enteritis—there was no thickening or edema of the wall. She underwent treatment with intravenous steroids which resulted in improvement of her clinical condition.[48]

Involvement of multiple abdominal organs should always raise suspicion of a systemic autoimmune reaction attacking smooth muscles. Histopathological examination of the gastrointestinal tract in patients with CIPO secondary to SLE revealed extensive myocyte necrosis in the muscularis propria with active inflammatory cell infiltrate, severe atrophy and fibrosis of the muscularis, active serositis with serosal thickening and fibrosis, little or no evidence of vasculitis or injury to bowel innervation, and absence of thromboembolic disease.[44-46] Necrosis involving the intestinal muscularis occurs without the typical vasculitis of SLE, as seen in other organs. A good response to immunosuppressive treatment may suggest a direct impact of antibodies affecting smooth muscle cells. It has been demonstrated that autoantibodies against proliferating cell nuclear antigen (PCNA) have been exclusively found in SLE patients, and there have been clinical cases reports in which patients with this antibody and systemic sclerosis developed CIPO.[49] While CIPO is rare in patients with SLE, ureter dilation and difficulty in urine drainage are much more common, but it is important to keep this in mind.

Systemic sclerosis (SSc) is a chronic autoimmune disease that attacks connective tissue. It leads to the fibrosis in internal organs and the skin, accompanied by extensive vasculopathy. About 90% of patients diagnosed with SSc, both in diffuse and limited forms, experience gastrointestinal problems, and these complications are most commonly observed in patients.[50,51] Symptoms are usually mild, but 8% of patients experience serious complications, significantly increasing mortality among SSc patients, one of which is CIPO.[52]

A clinical case of a woman with a past medical history of SSc is presented in literature. She was hospitalized due to progressively worsening constipation, vomiting, and regurgitation. Examinations revealed dilatation of the small and large intestine with air-fluid levels. She was treated successfully with intravenous hydration and pharmacotherapy, allowing oral feeding in small portions several times a day.[53]

The pathogenesis of systemic sclerosis is complex, involving immune system activation, vascular damage, and overproduction of collagen, which then deposits in connective tissue.[54, 55] The pathogenesis of gastrointestinal symptoms in patients with SSc is likely caused by changes that can be divided into four stages, which are: vasculopathy,

neural dysfunction, smooth muscle atrophy, and fibrosis.[56] Thanks to prokinetic agents, the functional abnormalities can be reversed but only in the first two stages. In the third stage, smooth muscle atrophy occurs, in causation to neurological dysfunction and the vasculopathy, only partial improvement can be achieved with pharmacological treatment. The final, fourth stage, is characterized by fibrosis, which is resistant to treatment.[53]

CIPO is rare but also occurs as a serious complication in patients with SSc. It is associated with approximately 7% of deaths in patients hospitalized for this cause.[57] Despite available treatment, it often leads to progression and patients usually experience a decreased quality of life.[53] Targeted therapy contributed to reduce motility rate in patients with SSc is not currently conducted and its treatment relies mainly on prokinetic agents, such as erythromycin and metoclopramide, as well as laxatives and occasional enemas.[58]

Conclusion

The purpose of this study is to summarize the available medical knowledge about the causes of CIPO in patients. It is important to remember how huge problem this disease is despite its rarity - between 10 and 25% of children with CIPO will die from their disease.[59] Searching for the cause of intestinal obstruction symptoms in a patient without a visible cause in imaging tests is a huge challenge for the clinician. We want to draw attention to the possible different causes of the symptoms and an individual approach to each case. Appropriate hydration, implementation of appropriate nutritional treatment for the patient, and then the use of available pharmacological treatment in accordance with the cause of the pathology, e.g. prokinetics, muscle relaxants, steroids, antibiotics or anticancer drugs. Unlike in the case of intestinal obstruction caused by a mechanical cause, surgery for a patient with CIPO is in most cases of no benefit and may lead to greater complications related to the surgical procedure.[10] Selecting an appropriate treatment method, depending on the cause may be crucial for improving the quality of life of patients [59], which we want to draw attention to in this article, at the same time emphasizing that we are dealing with a chronic disease that may accompany the patient for most of his life.

References

[1] Zenzeri L, Tambucci R, Quitadamo P, et al. Update on chronic intestinal pseudo-obstruction. *Curr Opin Gastroenterol.* 2020; 36(3): 230-237.

[2] Radocchia G, Neroni B, Marazzato M, et al. Chronic intestinal pseudo-obstruction: is there a connection with gut microbiota? *Microorganisms* 2021; 9(12): 2549.
[3] Besaw RJ, Smith MP, Zerillo JA, et al. Chronic intestinal pseudo-obstruction in a patient with metastatic gastro-oesophageal junction cancer receiving treatment with pembrolizumab. *BMJ Case Rep.* 2019; 12(12): e232388.
[4] Tanaka K, Ohkubo H, Yamamoto A, et al. Natural history of chronic intestinal pseudo-obstruction and need for palliative care. *J Neurogastroenterol Motil.* 2023; 29(3): 378-387.
[5] Izumi Y, Masuda T, Horimasu Y, et al. Chronic intestinal pseudo-obstruction and orthostatic hypotension associated with small cell lung cancer that improved with tumor reduction after chemoradiotherapy. *Intern Med.* 2017; 56(19): 2627-2631.
[6] Krasselt M, Exner M, Lübbert C. Ogilvie syndrome in disseminated tuberculosis. *Dtsch Arztebl Int.* 2019; 116(9): 145.
[7] Herdes RE, Cagil Y, Namjoshi S, et al. Initial presentation of a pediatric intestinal pseudo-obstruction episode after SARS-CoV-2 Virus (COVID-19) Infection. *JPGN Rep.* 2021; 2(2): e059.
[8] Sonsino E, Mouy R, Foucaud P, et al. Intestinal pseudoobstruction related to cytomegalovirus infection of myenteric plexus. *N Engl J Med.* 1984; 311(3): 196-197.
[9] Puig I, Champeval D, De Santa Barbara P, et al. Deletion of Pten in the mouse enteric nervous system induces ganglioneuromatosis and mimics intestinal pseudoobstruction. *J Clin Invest.* 2009; 119(12): 3586-3596.
[10] Antonucci A, Fronzoni L, Cogliandro L, et al. Chronic intestinal pseudo-obstruction. *World J Gastroenterol.* 2008; 14(19): 2953-61.
[11] Joshua Lederberg. Infectious History. *Science* 2000*;* 288: 287-293.
[12] Ategbo S, Turck D, Gottrand F, et al. Chronic intestinal pseudo-obstruction associated with cytomegalovirus infection in an infant. *Journal of Pediatric Gastroenterology & Nutrition* 1996; 23(4): 457-460.
[13] Debinski HS, Kamm MA, Talbot IC, et al. DNA viruses in the pathogenesis of sporadic chronic idiopathic intestinal pseudo-obstruction. *Gut.* 1997; 41(1): 100-106.
[14] Greenberg J, Greenberg J, Helmstetter N. Chronic intestinal pseudo-obstruction due to Strongyloides stercoralis. *IDCases* 2018; 13: e00425.
[15] Pessarelli T, Basilisco G, Spina L, et al. Intestinal pseudo-obstruction caused by Giardia lamblia infection. *BMJ Case Rep.* 2022; 15(11): e252319.

[16] Sinagra E, Pellegatta G, Maida M, et al. Could chronic idiopatic intestinal pseudo-obstruction be related to viral infections? *J Clin Med.* 2021; 10(2): 268.
[17] Carod-Artal FJ. The enteric nervous system: another forgotten autonomic target in viral infections? *Clin Auton Res.* 2017; 27(3): 137-138.
[18] Lee SW, Ko CW, Liao SC, et al. A case with vitamin D deficiency-induced cytomegalovirus enteritis presenting as bowel pseudo-obstruction. *Gastroenterology Res.* 2017; 10(3): 193-195.
[19] Besnard M, Faure C, Fromont-Hankard G, et al. Intestinal pseudo-obstruction and acute pandysautonomia associated with Epstein-Barr virus infection. *Am J Gastroenterol.* 2000; 95(1): 280-284.
[20] Pinto M, Dobson S. BK and JC virus: a review. *J Infect.* 2014; 68(1): 2-8.
[21] Selgrad M, De Giorgio R, Fini L, et al. JC virus infects the enteric glia of patients with chronic idiopathic intestinal pseudo-obstruction. *Gut.* 2009; 58(1): 25-32.
[22] Sinagra E, Raimondo D, Gallo E, et al. Could JC virus be linked to chronic idiopathic intestinal pseudo-obstruction? *Clin J Gastroenterol.* 2020; 13(3): 377-381.
[23] Chatila R, Kapadia CR. Intestinal pseudoobstruction in acute Lyme disease: a case report. *Am J Gastroenterol.* 1998; 93(7): 1179-1180.
[24] Gu L, Ding C, Tian H, et al. Serial frozen fecal microbiota transplantation in the treatment of chronic intestinal pseudo-obstruction: a preliminary study. *J Neurogastroenterol Motil.* 2017; 23(2): 289-297.
[25] Le TL, Galmiche L, Levy J, et al. Dysregulation of the NRG1/ERBB pathway causes a developmental disorder with gastrointestinal dysmotility in humans. *J Clin Invest.* 2021; 131(6): e145837.
[26] Bianco F, Lattanzio G, Lorenzini L, et al. Enteric neuromyopathies: highlights on genetic mechanisms underlying chronic intestinal pseudo-obstruction. *Biomolecules* 2022; 12(12): 1849.
[27] Skelton PD, Stan RV, Luikart BW. The role of PTEN in neurodevelopment. *Mol Neuropsychiatry* 2020; 5(1): 60-71.
[28] Panigrahi AR, Pinder SE, Chan SY, et al. The role of PTEN and its signalling pathways, including AKT, in breast cancer; an assessment of relationships with other prognostic factors and with outcome. *The Journal of Pathology* 2004; 204(1); 93-100.

[29] Hirano M, Carelli V, De Giorgio R, et al. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): position paper on diagnosis, prognosis, and treatment by the MNGIE International Network. *J Inherit Metab Dis.* 2021; 44(2): 376-387.

[30] Hirano M, Nishigaki Y, Martí R. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): a disease of two genomes. *Neurologist.* 2004;10(1): 8-17.

[31] Granero Castro P, Fernández Arias S, Moreno Gijón M, et al. Emergency surgery in chronic intestinal pseudo-obstruction due to mitochondrial neurogastrointestinal encephalomyopathy: case reports. *Int Arch Med.* 2010; 3: 35.

[32] Hirano M, Martí R, Casali C, et al. Allogeneic stem cell transplantation corrects biochemical derangements in MNGIE. *Neurology.* 2006; 67(8): 1458-1460.

[33] Fournier N, Fabre A. Smooth muscle motility disorder phenotypes: A systematic review of cases associated with seven pathogenic genes (*ACTG2*, *MYH11*, *FLNA*, *MYLK*, *RAD21*, *MYL9* and *LMOD1*). *Intractable Rare Dis Res.* 2022; 11(3): 113-119.

[34] Rana JS, Khan SS, Lloyd-Jones DM, et al. Changes in mortality in top 10 causes of death from 2011 to 2018. *J Gen Intern Med.* 2021; 36(8): 2517-2518.

[35] Koo MM, Swann R, McPhail S, et al. Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. *Lancet Oncol.* 2020; 21(1): 73-79.

[36] Thapa B, Mahendraker N, Ramphul K. Paraneoplastic Syndromes. 2023 Mar 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–.

[37] Sardiña González C, Martínez Vivero C, López Castro J. Paraneoplastic syndromes review: The great forgotten ones. *Crit Rev Oncol Hematol.* 2022; 174: 103676.

[38] Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. *Mayo Clin Proc.* 2010; 85(9): 838-854.

[39] Taverna JA, Babiker HM, Yun S, et al. The great masquerader of malignancy: chronic intestinal pseudo-obstruction. *Biomark Res.* 2014; 2(1): 23.

[40] Amiot A, Joly F, Messing B, et al. Pseudo-obstruction intestinale chronique et syndrome des anti-Hu : 13 ans de suivi sans apparition de néoplasie. *Gastroentérologie Clinique et Biologique* 2008; 32(1): 51-55.

[41] Lee HR, Lennon VA, Camilleri M, et al. Paraneoplastic gastrointestinal motor dysfunction: clinical and laboratory characteristics. *Am J Gastroenterol.* 2001; 96(2): 373-379.

[42] Wang PF, Chen Y, Song SY, et al. Immune-related adverse events associated with anti-PD-1/PD-L1 treatment for malignancies: a meta-analysis. *Front Pharmacol.* 2017; 8:730.

[43] Besaw RJ, Smith MP, Zerillo JA, et al. Chronic intestinal pseudo-obstruction in a patient with metastatic gastro-oesophageal junction cancer receiving treatment with pembrolizumab. *BMJ Case Rep.* 2019; 12(12): e232388.

[44] Perlemuter G, Chaussade S, Wechsler B, et al. Chronic intestinal pseudo-obstruction in systemic lupus erythematosus. *Gut* 1998; 43: 117-122.

[45] Mok MY, Wong RW, Lau CS. Intestinal pseudo-obstruction in systemic lupus erythematosus: an uncommon but important clinical manifestation. *Lupus* 2000; 9: 11-18.

[46] Hill PA, Dwyer KM, Power DA. Chronic intestinal pseudoobstruction in systemic lupus erythematosus due to intestinal smooth muscle myopathy. *Lupus* 2000; 9: 458-463.

[47] Pardos-Gea J, Ordi-Ros J, Selva A, et al. Chronic intestinal pseudo-obstruction associated with biliary tract dilatation in a patient with systemic lupus erythematosus. *Lupus* 2005; 14: 328-330.

[48] Park FD, Lee JK, Madduri GD, et al. Generalized megaviscera of lupus: refractory intestinal pseudo-obstruction, ureterohydronephrosis and megacholedochus. *World J Gastroenterol.* 2009; 15(28): 3555-3559.

[49] Nojima Y, Mimura T, Hamasaki K, et al. Chronic intestinal pseudoobstruction associated with autoantibodies against proliferating cell nuclear antigen. *Arthritis Rheum* 1996; 39: 877-879.

[50] Turner R, Lipshutz W, Miller W, et al. Esophageal dysfunction in collagen disease. *Am J Med Sci.* 1973; 265(3): 191–199.

[51] Akesson A, Wollheim FA. Organ manifestations in 100 patients with progressive systemic sclerosis: a comparison between the CREST syndrome and diffuse scleroderma. *Br J Rheumatol.* 1989; 28(4): 281–286.

[52] Gyger G, Baron M. Systemic Sclerosis: Gastrointestinal disease and its management. *Rheum Dis Clin North Am.* 2015; 41(3): 459–473.

[53] Shah J, Shahidullah A. Chronic intestinal pseudo-obstruction in systemic sclerosis: an uncommon presentation. *Case Rep Gastroenterol.* 2018; 12(2): 373-378.

[54] Black CM. The aetiopathogenesis of systemic sclerosis: thick skin--thin hypotheses. *The Parkes Weber Lecture* 1994. *J R Coll Physicians Lond.* 1995; 29(2): 119-130.

[55] Denton CP, Black CM, Korn JH, et al. Systemic sclerosis: current pathogenetic concepts and future prospects for targeted therapy. *Lancet* 1996; 347(9013): 1453–1458.

[56] Sjogren RW. Gastrointestinal features of scleroderma. *Curr Opin Rheumatol.* 1996; 8(6): 569–575.

[57] Valenzuela A, Li S, Becker L, et al. Intestinal pseudo-obstruction in patients with systemic sclerosis: an analysis of the Nationwide Inpatient Sample. *Rheumatology* 2016; 55(4): 654–658.

[58] Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. *N Engl J Med.* 1991; 325(21): 1461–1467.

[59] Zhu CZ, Zhao HW, Lin HW, et al. Latest developments in chronic intestinal pseudo-obstruction. *World J Clin Cases.* 2020; 8(23): 5852-5865.