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Rare clinical presentations and advances in the treatment of Buerger's disease - narrative review

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Abstract

Introduction

Buerger's disease (BD) is an inflammatory disease with an etiology that is still not fully understood. It involves venous and arterial vessels, of small and medium caliber, of the lower and upper extremities (Cacione et al., 2020). This inflammation predominantly affects young, tobacco-smoking men, usually those before the age of 40. Literature data relating to peripheral arterial disease in general, put the prevalence of BD at between 0.5%-5.6% in Western European countries (Liu et al., 2023; Öztan et al., 2023). In this paper, we summarized the latest literature reports on rare clinical images and new directions in the treatment of Buerger's disease.

Aim of the study

The purpose of this systematic review was to compile the latest literature on the etiology, atypical disease presentation, associations with other diseases and modern treatment of Buerger's disease.

Materials and methods

The materials used by our team were obtained from a review of the currently available literature in the PubMed database. To search for articles, we used keywords such as: Buerger's disease, thromboangiitis obliterans, thrombosis, atherosclerosis, Peripheral arterial disease, vasculitis.

Conclusion

In addition to its characteristic clinical presentation, Buerger's disease can present under a number of atypical forms. Such examples, less common conditions in the course of BD are intestinal vascular involvement mimicking the condition of acute abdomen, infertility condition due to gonadal involvement in the patient, possible correlation between the level of ASA (anti-sperm antibodies) and reduced fertility, the occurrence of nail lesions, renal complications, including the nephrotic syndrome, ocular or psychiatric manifestations. It is important for the clinician, in the diagnostic and therapeutic process at the onset of the described symptoms, not to exclude the possibility of an uncommon course of BD, to make a correct diagnosis and undertake optimal treatment.

Keywords: Buerger's disease; thromboangiitis obliterans; thrombosis; atherosclerosis; peripheral arterial disease; vasculitis.

Introduction

Buerger's disease (BD), otherwise known as TAO - thromboangiitis obliterans, is a rare segmental inflammatory disease of small and medium-sized peripheral vessels with a thromboembolic origin usually affecting the upper and lower extremities. The prevalence of the disease among all patients with peripheral arterial disease ranges from a value of 0.5 to 5.6% in Western European countries to a value of 45% - 63% in India (Cacione et al., 2020; Öztan et al., 2023). Symptoms that can occur in the course of BD depending on the severity are most

commonly intermittent pain in the fingers and toes and pain on the fingertips, hypersensitivity to cold, claudication, Raynaud's sign. More often these symptoms are experienced by ANA/RF positive patients (Shapouri-Moghaddam et al., 2021). Other researchers, however, mention ulcer, rest pain and gangrene as the most common symptoms (Salimi et al., 2022). The etiology of this process is still unclear, unrelated in pathogenesis to the atherosclerotic process, but it is certain that there is an association of a higher incidence and progression of this condition in young men, under 40 years of age and smokers compared to non-smokers. However, the presence of this process cannot be forgotten also in women, adolescents and the elderly in whom the incidence of the disease increases over the years, (Shapouri-Moghaddam et al., 2021). Referring to sources, up to 95% of cases of this disease occur in young smokers. (Gupta et al., 2021). The most common associated diseases are arteriosclerosis, diabetes mellitus, heart disease or cerebrovascular disease (Watanabe et al., 2024). There are papers linking the occurrence of BD to Rickettsia infection (Chung et al., 2022). BD appears to have no definitive treatment (Shapouri-Moghaddam et al., 2021). Smoking cessation is key to halting the progression of the disease, (Jaroonwanichkul et al., 2023; Kim et al., 2023) however, smoking other drugs or chewing tobacco is also linked to a higher incidence of BD (Choi et al., 2020). Patients may also benefit clinically through the use of targeted endovascular therapy, potentially preventing amputations and accelerating wound healing (Sharebiani et al 2020). It has been hypothesized that there is a genetic predisposition to tobacco hypersensitivity due to the presence of a particular HLA subtype along with adrenergic dysfunction and an altered peripheral sympathetic nervous system response to tobacco smoke (Shapouri-Moghaddam et al., 2021). Increased biomarkers of oxidative stress, such as SOD, MDA, and CoQ10, are also observed in patients, making this a promising and modern approach to BD in preventive medicine (Sharebiani et al., 2020). Noticeably more often BD is diagnosed in people living in Eastern Europe, the Balkans, Israel and Asian countries in particular (Harwood et al., 2023). Ultimately, the disease leads to significant loss of patient function, disability and often the need for amputation of the fingers affected by the necrotic process (Ziaeemehr et al., 2022; Starace et al., 2022, Qaja et al., 2023). Nationwide data from Korea report a 10-year survival rate with BD estimated at about 65% (Choi et al., 2020).

Methodology

In this work, the queries requested by our research team were based on the principles of preferred reporting elements for systematic reviews. We used the free PubMed database as the main source of literature data. The study consisted of searching the database using keywords such as Buerger's disease, thromboangiitis obliterans, thrombosis, atherosclerosis, peripheral arterial disease, and vasculitis. The articles were initially selected on the grounds of title, then on the abstracts. All of the literature we cited is no older than 2020. We extracted the articles in two teams for proper selection of materials.

Current reports of atypical presentations of Burger Disease

Reproductive system

There is little information in the literature describing BD involvement of the reproductive organs and resulting in disruption, or deprivation, of the patients' fertility. In addition to the occurrence of few cases of BD in the vas deferens, penis, or a single report of BD in the testicle, a group of researchers from the US described the case of a patient, with no specific physical symptoms and no significant medical history, who had complained of increasing pain in the left testicle for two weeks. The presence of a mass within the testicle was demonstrated, which it was decided, due to the difficulty of differentiating the lesion from a neoplastic process, to excise. In the histopathological examination performed, it turned out to be BD. The patient had been an active smoker of marijuana and cigarettes for 25 years (Harwood et al., 2023).

In contrast, other researchers have observed that by the time BD is diagnosed, the patient is generally already infertile. They conducted a study in 39 Caucasian men with BD vs. a control group, of the levels of ASA, testosterone, luteinizing hormone LH and folliculotropic hormone FSH. There was a significant elevation of ASA (anti-sperm antibodies) levels in 25.6% of patients ($p= 0.003$, $CC= 6.96$), which may suggest a correlation of the incidence of secondary infertility in BD patients with ASA levels. (Ziaeemehr et al., 2022).

Nail lesions

Other examples of rare pathological processes that can occur in the course of BD as the first symptom are nail changes, such as chronic paronychia, proximal leukonychia, onycholysis, or nail bed erosion. It is therefore important for dermatologists to be aware of the possible course of BD with nail plate involvement and to recognize the condition early and refer patients for appropriate treatment (Starace et al., 2022).

Nephrotic syndrome

Nephrotic syndrome is another example of rare BD. The case of a patient diagnosed with nephrotic syndrome, renal dysfunction and mild hypertension of 150-170/80-100 mmHg on the background of FSGS, with confirmed glomerular lesions was first reported in Japan. On admission, the patient was found to have proteinuria of 15 g/g creatinine, GFR of 45.2 mL/min/1.73m2, and decreased blood albumin levels to 2.8 g/dL. FSGS most likely developed due to BD-associated renal microinfarction, according to investigators (Yamaguchi et al., 2022).

Gastrointestinal system and postoperative skin necrosis

BD-associated lesions can manifest with intestinal involvement, which occurs in about 2% of cases. The rarity of this course of the disease, as well as the symptoms raising suspicion of an acute abdomen due to mesenteric ischemia in a large proportion of cases, can lead to a delay in the application of appropriate treatment, an increase in patient morbidity and mortality. Mishra and his team described the case of a 45-year-old patient presenting with diffuse abdominal pain with attacks of vomiting and lazy bowel movements, following a right foot amputation four years earlier. The patient had undergone multiple surgeries and died on the 23rd postoperative day due to septic complications. This case shows that the occurrence of acute abdominal symptoms in a young smoker, especially with a history of amputation from non-traumatic causes, should raise suspicion of intestinal TAO (Mishra et al., 2021). Another example concerning BD issues in surgery is the possibility of postoperative skin necrosis. Thus, in the case of non-healing chronic wounds, especially in young and habitual smokers, BD should be kept in mind as a potential cause of this process (Choi et al., 2020).

BD in the elderly

BD in elderly patients is rarely reported in the literature. It is worth mentioning that patients over 50 years of age are often included in the atherosclerotic process and other comorbidities, which is a factor that can cause diagnostic difficulties and also worsen the prognosis of patients. Iwai and his research group described the cases of three patients, aged 71, 74, 82, each experiencing a history of claudication, and burdened with hypertension, hyperlipidemia and diabetes mellitus, respectively. An interesting observation is that each patient had dental cavities (Iwai et al., 2022).

Ophthalmic symptoms

Information on ocular manifestations in BD patients is still limited in the literature, and they are an extremely rare complication of the disease. A paper (Szydełko-Paśko et al., 2022) based on 13 articles describes the ocular problems that can occur in BD. These include non-arteritic anterior ischemic neuropathy of the optic nerve (NAION), occlusive retinal vasculitis and

periphlebitis, papillophlebitis, central retinal artery occlusion (CRAO), branch retinal artery occlusion (BRAO), normal tension glaucoma (NTG), uveitis, chorioretinal atrophy, retinitis, papillitis, optic nerve atrophy, and changes typical of hypertensive retinopathy. These changes are observed extremely rarely in BD patients, moreover, there are no specific methods to predict their occurrence in this group of patients. Thus, it should be kept in mind that any patient affected by BD is predisposed to develop ocular complications.

Psychiatric disorders

The case of a 33-year-old patient, a habitual smoker, experiencing progressive lower extremity claudication since the age of 22 (all inflammatory, autoimmune and atherosclerotic markers were negative), who developed secondary psychosis due to CNS involvement, refractory to treatment with neuroleptics, illustrates how insidious the course of BD can be. Psychosis of organic origin can mimic psychosis of primary origin, thus delaying diagnosis and treatment. The frequency of psychiatric disorders in the course of BD is unknown and their characteristics remain a poorly studied issue, but awareness of the possibility of such a course of BD is crucial in the diagnostic and therapeutic process (Awara et al., 2023).

Reports of innovative BD therapies

Most important in the therapeutic process of BD is immediate smoking cessation. This attitude of the affected patient is crucial and, in many cases, the only one to halt the progression of the disease. However, even smoking restriction alone can lead to clinical benefits. In addition, there are case reports of patients in whom reducing smoking by half allowed ulcerated limb lesions to heal and reduce pain (Jaroonwanichkul et al., 2023). Patients affected by BD-related limb claudication may benefit even with supervised exercise therapy (SET) (Komiya et al., 2023).

It has been postulated that the immune system is involved in the development or progression of BD through oxidative stress, T-cell-associated immune damage, IL-33 release, MyD88-dependent TLR signaling pathway, sympathetic ganglia inflammation, COX inflammatory pathway, impaired collateral artery development by IFN-γ and VEGFR1, and HMGB 1. Careful study and identification of the molecular pathways contributing to BD may lead to new molecular therapies that can restore the immune homeostasis disrupted during the disease (Shapouri-Moghaddam et al., 2019).

Angiogenic BD therapies are currently being described. In particular, injections of DNA material, viruses in the form of naked DNA plasmids, viral gene constructs whose genetic material is expressed causing angiogenesis, and stem cell-based approaches that have a regenerative effect on blood vessels and wound tissue. Work on cell-free exosome-based approaches for therapeutic angiogenesis, and autologous implantation of bone marrow

mononuclear cells, BM-MNCs, seems promising (Ejiyooye et al., 2022; Fujioka et al., 2023; Yanishi et al., 2020). There are also reports of the efficacy of the Chinese herb mixture Si-Miao-Yong-An (SMYAD) in relieving pain and slowing the progression of BD, acting as an anti-inflammatory by lowering IL-6 and MMP9 and increasing the expression of angiogenic VEGF (Zou et al., 2023).

Conclusions

Burger's disease, in addition to its characteristic clinical picture, which should be differentiated from antiphospholipid syndrome and pregnancy, atherosclerosis, frostbite, giant cell arteritis, gout, nodular arteritis, Raynaud's syndrome, scleroderma, systemic lupus erythematosus, types 1 and 2 diabetes mellitus (Qaja et al., 2023), can run under many atypical forms. Such examples, less common conditions in the course of BD, described by our team, are involvement of the intestinal vasculature mimicking an acute abdominal condition, causing infertility due to involvement of the patient's gonads, occurrence of infertility in a high percentage at the time of BD diagnosis and a possible correlation between ASA (anti-sperm antibodies) levels and reduced fertility in these patients, occurrence of nail lesions, renal complications, including development of nephrotic syndrome, ocular or psychiatric manifestations. It is important for the clinician, in the diagnostic and therapeutic process at the onset of the described symptoms, not to exclude the possibility of an unseen course of BD, to make the correct diagnosis in time and undertake optimal treatment.

Authors' Contributions:

Conceptualization was done by Damian Chruścicki; methodology by Marcin Pelc; software by Wojciech Płonka; checking by Marta Żerek, Gracjan Sitarek; formal analysis by Wojciech Kulej; investigation by Damian Chruścicki; resources by Gracjan Sitarek; data curation by Jakub Waszczyński; writing - rough preparation by Paulina Bednarczyk; writing - review and editing by Marcin Pelc and Damian Chruścicki; visualization by Jakub Waszczyński; supervision by Wojciech Kulej; project administration by Wojciech Płonka; and receiving funding by Paulina Bednarczyk

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