Łanowy Patrycja, Ślusarz Krystian, Dzindzio Jakub, Pyka Weronika, Bichalski Miłosz, Blaszkowszka Maria, Jaroszewicz Jerzy. Actinomycosis - forgotten disease as a diagnostic challenge. Journal of Education, Health and Sport. 2019;9(5):256-264. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.2901660
http://ojs.ukw.edu.pl/index.php/johs/article/view/6922

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 28.04.2019. Revised: 28.04.2019. Accepted: 18.05.2019.

Actinomycosis - forgotten disease as a diagnostic challenge

Patrycja Łanowy[1], Krystian Ślusarz[1], Jakub Dzindzio[1], Weronika Pyka[1], Miłosz Bichalski[1], Maria Blaszkowszka[1], Jerzy Jaroszewicz[1*,]

[1]Department of Infectious Diseases and Hepatology in Bytom, Medical University of Silesia, Poland
E-mail addresses: 1patrycjalanowy@gmail.com, 1milosz.bichalski@gmail.com, 1jakfradzi@gmail.com, 1sluszarzkrystian@gmail.com, 1pyka.weronika@gmail.com, 1maria.blaszkowska@gmail.com,
1*Coressponding author: jjaroszewicz@sum.edu.pl

ABSTRACT

Actinomycosis is neglected, uncommon disease caused by bacteria. The greatest difficulty in correct and early diagnostics of actinomycosis is the fact that it often mimics other conditions. The difficulties in diagnostic of actinomycosis result in misdiagnosis, lengthening the patient's treatment time, unnecessary surgical treatment and sometimes dangerous complications.
Aim of the article: The aim of the article is to familiarize readers with the rarest conditions that have been mistaken for actinomycosis.

KEYWORDS: actinomycosis, diagnostic difficulties, misdiagnosis, malignancy mimicking tumor

INTRODUCTION

Human actinomycosis is an neglected, rare granulomatous disease. This typically slowly progressing disease, which may be chronic or subacute, is caused by Gram-positive, mostly ana-aerobic bacteria from Actinomyces genus. Actinomycosis may be caused by almost 20 species of pathogenic to human bacteria. [1,2,3] The major part of the cases is caused by Actinomyces israeli or Actinomyces gerencseriae. Other causative agents include A. naeslundi, A.meyeri, A visconus or A. turicensis. [2,3,4]

Bacteria from this genus occur as a part of commensal bacterial flora of organism, which colonization of the surfaces begin in early childhood. Causative Actinomyces species are commonly found on the vaginal mucosa, in the oral cavity, on the skin or in the intestine. [5]

The most common clinical type of Actinomycosis is cervicofacial, which may concern tonsils, jaw or even the tongue. This disease may also occur in the lungs (pulmonary type), intestine and liver (abdominal type), ovary (pelvic type). In extremely rare cases Actinomycosis may affect the nervous system or muscle tissue [1,2].

Mostly infection is diagnosed in immuno-compromised patients. The most vulnerable are patients with risk factors like intrauterine device, malnutrition, alcoholism, poor oral hygiene, diabetics, patients after recent surgery or with injuries [2,4].

EPIDEMIOLOGY

Actinomycosis is considered a rare disease, but the epidemiological data are not known, however, it is more common in areas with low socioeconomic status [6,7,8]. No higher incidence is observed in specific races [8,9]. The male to female ratio is 3:1 and the peak incidence ranges from 40 to 50 years of age [8]. Apart from gender and age risk factors include diabetes, immunosuppression caused by steroids, bisphosphonates, leukemia with chemotherapy, HIV- infection, lung and renal transplant receipt, alcoholism, low oral hygiene and local tissue damage caused by trauma, recent surgery, irradiation [7]. The most frequently isolated species of the genus Actinomyces in cases of actinomycosis are A. israelii, A. gerencseriae and A. graevenitzii [6,10,11].

DIAGNOSTICS

Imaging studies. Diagnosis of actinomycosis is often difficult due to nonspecific clinical and radiological symptoms [12]. The proper diagnosis at first presentation is rather rare and the initial diagnoses are usually neoplastic diseases or bacterial infections – such as tuberculosis, pneumonia or lung abscess [13,14]. Delay in the diagnosis seems to increase the risk of death and generate unnecessary investigation costs. Imaging studies may help to distinguish malignancies from actinomycosis [15]. In the early stages of infection, imaging studies (such as computed tomography or magnetic resonance imaging) most often reveal tumors and non-specific abscesses, which allow to precisely determine the anatomical location and can be helpful when collecting the tissue for examination [6,8,12]. In later stages, the infiltration of surrounding tissues can be noticed [7]. In case of an acute form of the most common actinomycosis (cervicofacial), the images of computed tomography depict soft tissue swelling, a necrotic mass lesion, or a pyogenic abscess. In a chronic form, the pathological mass may spread to the skin, which can be accompanied by draining sinus tracts [15,16].

Blood tests. The laboratory data are also non-specific. They reveal changed inflammatory parameters - mild leucocytosis, an elevated level of C-reactive protein and increased erythrocyte sedimentation rate [17,18]. In some cases, high platelet count or anemia are noticed [17,19]. Total bilirubin and alkaline phosphatase concentration may be mildly elevated in hepatic actinomycosis [20].

Histological examination. Histological examination is one of the most useful tests in the diagnostics of Actinomycosis. Typical microscopic findings include 'sulfur granules'. These are clusters composed of tangled filaments of Actinomyces species with cell and tissue debris, accumulating calcium compounds. Neutrophils, giant cells, plasma cells can be observed around these grain [21]. The whole structure is stabilized by protein-polysaccharide complex, which protects them against phagocytosis [6]. Gram, Giemsa or Gomori methenamine-silver staining can show Gram-positive filaments branching at the bounds of granules [7]. Almost 75% histological examination averaged the number of 'sulfur granules' is one to three [6]. Some of the microscopic slides have any single granules because they are destroyed when creating preparations. Therefore, not finding 'sulfur granules' cannot rule out the diagnosis [22].Should be taken into account that sulfur grains are characteristic (but not pathognomonic) for Actinomyces spp. They also occur in diseases such as nokardioza, chromomycosis, botryomycosis, eumycetoma, infections caused Streptococcus or Streptomyces [21, 22].

Serology. It is also possible to recognize Actinomyces spp. by reacting with specific antibodies, even when the preparation has been inserted into formalin. This technique has high specificity and is an accurate solution for mixed infections [7].

Microbiology. Actinomyces is Gram-positive, filamentous, branching, nonacid-fast, non-spore forming, anaerobic or microaerophilic [7,16,21]. It grows on chocolate agar, broth, Brucella blood Agar with the addition of hemin and wit. K. The culture should be provided in an atmosphere of 6-10% CO2 at 37 ° C. Colony creation time is about 14 days. Actinomyces colony appearance depends on the type of culture media: on the solid, it has the appearance of a 'molar tooth' but in the liquid one a 'breadcrumb' [15]. Breeding should be based on tissue aspirations, pus, tissues. Urine, sputum or bronchoscopy should be avoided. Growing Actinomyces bacteria is the final confirmation of the diagnosis. However, a positive breeding result is achieved in only 50% of cases. The reason for this may be earlier antibiotic therapy, contamination with physiological flora, poor breeding conditions, too short incubation time [6]. Commercial biochemical kits achieve the low efficacy of <60% [7].

Molecular methods, i.e. sequencing of 16rRNA or MALDI-TOF may turn out to be faster and much more effective diagnostic methods, and the results of research on these methods are promising [6].

SIGNS AND SYMPTOMS

The vast majority of Cervicofacial actinomycosis have an odontogenic origin and concern the perimandibular regions. Signs as pain, fever and immediate formation of abscesses indicate the acute course of the disease which is rare. In typical, chronic type of disease symptoms are quite the opposite. Slowly growing abscesses with drainage of sinus tracts on the surface of the skin or oral mucosa, sometimes expressing a typical thick yellow effusion with characteristic sulfur granules [6,7,23,24,25,26,27]. Interestingly, enlarging the lymph nodes is also rare, moreover, bone lesions occur in 1 out of 10 cases only. Imaging findings are usually useless in the correct diagnosis [6].

Signs of respiratory tract actinomycosis are non-specific. Most common are cough and shortness of breath. However, sputum stained with blood also may be a clinical manifestation of actinomycosis in that specific location. This may lead to the at first incorrect diagnosis of the disease like tuberculosis or a tumor - especially when radiological findings are apparently unchanged [6,28]. As the disease progresses cavitation and sinus tract may occur. In those cases, patients should be examined for actinomycosis [6,29,30]. Additionally, cutaneous and muscular abscesses can be found due to Pulmonary Actinomycosis [31].

Extrafacial bone and joint actinomycosis symptoms are non-characteristic. Signs imitate chronic bone and joint infection [6,32].

Genitourinary tract actinomycosis may be associated with the use of an intrauterine device and previous surgical procedures, while symptoms such as pain, vaginal discharge, dysuria, haematuria or constipation are not straightforward [9,33]. Those signs along with radiological findings mostly indicate bladder carcinoma, uterine myoma, gynecological malignant tumors or adenomyosis rather than actinomycosis [6,9,33].

In the central nervous system, actinomycosis appears with symptoms such as convulsions, focal weakness, sensory losses [6]. Non-characteristic signs also appear in digestive tract actinomycosis and they depend on where the bacteria is located. Forex: dysphagia mostly happened to patients with ulcerative esophagus; palpable mass along and pain - appendix; and so on [6,19].

In cutaneous actinomycosis, the symptoms are similar to some more frequent skin diseases such as skin mycosis, chronic dermatitis or mycobacteriosis. Over time, nodular changes with fistulas, abscesses or cold mass may appear on the skin [6,34,35].

TREATMENT

In the treatment of actinomycosis, high doses of antibiotics are used for a sufficiently long time (2–6-week intravenous therapy + 6–12-month oral therapy), what reduces the chances of relapse [15]. In most cases, it is not necessary to use antibiotics with a very wide spectrum of action in order to affect other potential co-infections [36,37].

In a study conducted in Denmark, the resistance of thirty-four Actinomyces strains to some antimicrobial agents belonging to different groups was compared. Benzylpenicillin, piperacillin/tazobactam, erythromycin, linezolid, and tigecycline were antibiotics for which no strain was resistant [38]. Amoxicillin/clavulanic [39,40] and doxycycline [41] also play a role in treatment. In turn, antibiotics that are not adequate for the treatment of actinomycosis due to poor or no activity, include metronidazole, aminoglycosides, fluoroquinolones aztreonam, or co-trimoxazole [38,42]. In cases where necrotic lesions, abscesses, fistulas or obstructions are involved, antibiotic therapy may be supported by surgical treatment [43].

MISTAKEN DIAGNOSIS

In our department, 6 cases of Actinomycosis were diagnosed in 5 years. Interestingly enough, only two-thirds were diagnosed with a less common abdominal type of actinomycosis. Also, in opposite to data found in literature about men to women ratio - all of our patients were women. Due to the difficulties in diagnosis and non-specific symptoms - on the two-thirds of the patients were performed surgery of infected organs, before the correct diagnosis was set.

Pusitol et all. describe a case report of the patient with IUD, in which computed tomography scan examination exposed mass in abdominal and pelvic, which ascend (among others) colon, ileum, ovary, and uterus. The patient was referred for surgical treatment due to malignancy neoplasm suspicion. Also during laparoscopy mass looks like malignancy neoplasm. Histopathological examination of the material collected during surgical procedure allowed to make a correct diagnosis. After that patient was treated for six months with penicillin and fully recovered [44].

A rare case of actinomycosis of primary urachal was described Sithika et all. A 50-years-old patient with abdominal pain report to the hospital. Physical examination revealed a palpable mass in the suprapubic area. Imaging diagnostic reveals that mass may potentially infiltrate and damage bowel loops. Due to these facts, the patient was suspected with urachal carcinoma and referred for surgical treatment of extinction of the mass, part of the bladder and potentially infiltrated ileal segments. Also in this case histopathological allowed the

proper diagnosis - examination of collected during this procedure reveal actinomycotic colonies. The patient fully recovered after intravenous penicillin treatment [45].

The rare case of actinomycosis was described by Siddiq et all., 60-year-old woman came to the hospital with swollen, painful tongue with reduced mobility. There were no injury of the tongue in the patient's history. At first, she was suspected with a malignant tumor. The biopsy reveal actinomytic colonies, what allows to apply appropriate treatment with amoxicillin for 4 weeks. The patient fully recovered [46].

Another case concerns a 10-year-old girl with a complex medical history including asthma, recurrent sinus infections, methicillin-resistant staphylococcus and allergies. The patient reported pain and swelling of the right part of the neck, which lasts for 2 weeks, and the interview implies a recent infection of the upper respiratory tract. Imaging diagnostic methods reveal the superficial inflammatory mass of soft tissues. Intravenous clindamycin therapy was applied, but no positive results were obtained. Diagnostic include biopsies of the lesion and microbiological tests of the purulent liquid inside the lesion. The culture growth reveals among other things, Actinomyces odontolyticus. Patient started oral therapy with amoxicillin, but after a week the erythema occurs around the lesion. Due to this fact, therapy was changed on penicillin G - - firstly applied intravenously for 6 weeks, and then for 6 months orally [47].

The last case report concerns a 14-year-old boy who felt ill and fell to the ground while drinking an energy drink. Reanimations were carried out for one hour and death was confirmed. Previously, he complained for two weeks of chest pain, fatigue coughing and low temperature. The day before the incident, he reported to the doctor who diagnosed him with flu and recommended tylenol and aspirin. Additional tests have not been carried out. The performed section of the patient showed inflammation, emphysema and pulmonary edema in the macroscopic image. The posterior left ventricular wall had an atherosclerotic region that may indicate a scar after myocardial infarction. Signs of disease within the head and neck were excluded. A microscopic examination revealed lung inflammatory granulomas from A. Israelii, whereas in the heart acute myocardial infarction, chronic inflammation, and heart failure were established as the cause of sudden death [48].

CONCLUSIONS

Actinomycosis in highly developed countries is sporadically met, which is why doctors consider this ailment as forgotten. In addition, diagnostics creates many problems. The repeated attempts to culture the organism in most cases are unsuccessful, and the final diagnosis is established by multiple often ineffective histopathological examination. That illness can mimic neoplastic changes and is unnecessary "treated" surgically. Actinomycosis can be misdiagnosed at the first presentation because of the appearance of clinical and radiological manifestations similar to other, more widespread, diseases. The pathogen gives a range of symptoms reminiscent of cancer, what considerably delays the implementation of proper and effective treatment. Moreover WHO does not maintain statistics in terms of morbidity on actinomycosis. Doctors have to be more sensitive to the possibility of the patient having actinomycosis, thanks to which it will be faster to start proper treatment to prevent further progression of the disease.

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