Differential Diagnosis:

Case report

A 33-year-old Caucasian woman was found lifeless sitting on a park bench. After initially successful cardiopulmonary resuscitation by an emergency medical doctor the woman was taken to a hospital. Clinical laboratory examination at admission revealed that ethanol, methadone and benzodiazepine were present in her blood. The woman died three days later despite intensive care. Police investigation ascertained that she had suffered from alcoholism but her previous medical history seemed unremarkable.

At medico-legal autopsy, the external examination of the body showed several fresh puncture marks on the neck and arms as signs of recent medical treatment. Internal examination revealed hypoxic brain damage, characterized by a pale and massively swollen brain (weight 1420 g) with loss of clear-cut demarcation between the cortex and medulla on examination of multiple brain sections. In addition, massive pulmonary edema and fatty liver were observed. However, the most notable finding was a so-called “cobblestone” appearance of the mucosa of the ascending colon which was formed of linear ulcerations, edematous nodular swelling and inflammation of the bowel wall (**Fig. 1**). Except for the ascending colon, such lesions were not noticed in other parts of the digestive tract. Neither the finding of obstructive ileus nor peritonitis was observed. No underlying malignancies of the gastrointestinal tract were found. Histopathology of the ascending colon showed mucosal ulceration and *transmural* inflammation, affecting all layers of the bowel wall, consisting of nodular aggregates of chronic inflammatory cells (lymphocytes, plasma cells and histiocytes) with no caseation but hyaline deposits (*noncaseating granuloma*), massive edema, accumulation of partially hyalinized collagen and fibrosis (**Fig. 2**). These findings were compatible with the diagnosis of Crohn’s disease. Toxicological analysis was negative given the fact that the woman survived for three days in hospital.

The cause of death was fatal hypoxic brain damage secondary to coma probably due to combined effects of ethanol, methadone and benzodiazepine.

Discussion

"Cobblestone" appearance of the bowel mucosa, consisting of ulcerations demarcating areas of inflammatory edematous mucosa, is a well known macroscopic hallmark of Crohn's disease. However, encountering such lesion is extremely rare in both clinical endoscopic as well as autopsy practice. Crohn's disease is defined as a chronic, relapsing inflammatory condition that usually manifests in adolescents or young adults and is most common among Caucasians with a slight female predominance (up to 1.6:1) [1, 2]. The precise cause of Crohn's disease remains unknown, although numerous studies have suggested a variety of pathogenetic factors such as heredity, infectious agents, impairment of immune systems, environmental factors (e.g., smoking, lack of breast-feeding, dietry factors) and emotional stress [1-3]. Crohn's disease can affect any part of the digestive tract from oral cavity to anus, but occurs most frequently in the ileum and cecum (about 50%); in contrast, lesions limited to the colon, as observed in our case, is seen in only about 20% of the patients [1].

At autopsy as well as in clinical practice, Crohn's disease has to be differentiated from other inflammatory bowel diseases exhibiting similar symptoms such as ulcerative colitis, Behcet disease, intestinal tuberculosis, diverticulitis, and bacterial or viral gastroenteritis. Gross inspection at endoscopy with biopsy sampling and subsequent histopathological examination usually leads to the correct diagnosis. Although the typical "cobblestone" appearance as seen here is most valuable for the diagnosis of Crohn's disease, its observation is restricted to cases with moderate-to-severe inflammation and/or cases with a long-term diesease history [1-3]. In our case, the "cobblestone" appearance was strongly developed most probably because the woman suffered from the disease for a long period of time without appropriate medical treatment. Microscopic hallmarks of Crohn's disease that can be observed from the earliest stage of the disease include (i) neutrophil-mediated cryptic damage with the formation of focal cryptic abscess and (ii) chronic inflammation of all layers of the bowel wall (*transmural* inflammation) with *noncaseating granulomas* [1, 3]. The latter finding was also observed in our case. In addition, discontinous inflammation, referred to as "skip" areas; that is, segments of inflamed tissue which are separated by apparently normal tissue, is also a specific character of Crohn's disease [1]. The finding was not observed in the ascending colon in our case.

Although the clinical manifestation of Crohn's disease depends on the anatomical localization of the disease, the most common symptoms are abdominal pain, diarrhea (sometimes hematochezia), and recurrent fever [1, 2]. We hypothesize that the woman in our case must have had no such significant symptoms and therefore Crohn's disease was not diagnosed during her lifetime because alcohol and/or drug abuse with the resulting analgesia and indifference may have masked these

symptoms. In illegal drug abusers, diagnosis for organic diseases including brain abscess and endocarditis as well as inflammatory bowel disease (e.g., Crohn’s disease, ulcerative colitis) are occationally delayed or made only retrospectively by autopsy because of similar reasons [4, 5].

Crohn's disease is rarely a direct cause of death, but it can unexpectedly lead to fatal outcome when severe intestinal complications such as intestinal obstruction (resulting in obstructive ileus) or fistula/perforation (resulting in peritonitis, sepsis) as a sequal of the deep mural ulceration, or gastrointestinal cancer, occur during its course [6-8]. None of these complications from Crohn’s disease were observed in the present case and the cause of death was unrelated to the progress of Crohn’s disease here.

The present case report not only presents the characteristic “cobblestone” appearance of Crohn’s disease but also corroborates the importance of suspecting the presence of undiagnosed organic diseases in alcohol and/or illegal drug abusers, even if the deceased is a young female and it seems obvious that the cause of death is associated with substance abuse.

Conflict of interest statement

None declared.

References

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Figure legends:

Fig. 1: Gross appearance of the native mucosa of the ascending colon at autopsy. **a** The mucosal surface of the colon shows a “cobblestone” appearance due to the presence of linear ulcerations, edema and inflammation of the bowel wall. **b** Closer view of **a**.

Fig. 2: Histopathology of the ascending colon. **a** Mucosal ulceration (right), submucosa thickened by massive edema and nodular aggregates of chronic inflammatory cells (arrow). **b** Higher power view of mucosal ulceration with massive infiltration of leukocytes. **c Submucosal *noncaseating granuloma* with epitheloid cells and lymphocytes, plasma cells, histiocytes and partial hyalization. d** Fibroblasts and fibrosis forming scar tissue within the bowel wall. HE staining; original magnifications: **a, x2.5; b, x5.0; c, x20; d, x10**.