Hodgkin’s disease: Bacterial etiology very probable

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Abstract

Background: The etiology of Hodgkin’s disease is still unknown more than 180 years after its original description. In recent years a viral etiology was the preferred hypothesis. Epidemiological, clinical, laboratory, and histological findings, however, point rather to a bacterial etiology.

Materials and methods: In the histological work-up of tissues from patients suffering from Hodgkin’s disease periodic acid-Schiff (PAS) stains are routinely done. In several bacterial infections intracellular PAS-positive material can be observed.

Here ten PAS-stained slides per patient by magnifications of at least × 1000 of six Hodgkin patients were examined (24 000 cells per slide).

Results: PAS-positive diastase resistant intracellular rods and spheres were found in all Hodgkin patients but not in other malignant lymphomas.

Conclusions: The diastase resistant PAS-positive structures are compatible with intracellular bacteria. After gastric MALT-lymphoma and gastric non-cardia adenocarcinoma it appears that Hodgkin’s disease may also be a human tumor related to bacteria.

Introduction

During the last few years the discussion about the bacterial etiologies of malignant tumors was revived. In Xenopus a mycobacterium was shown to be related to a lymphosarcoma [1]. In mice a helicobacter species was found to be a likely candidate for the etiology of hepatocellular tumors [2]. A connection of bacteria to human neoplasms was shown for gastric MALT-lymphoma [3-5] and etiology of hepatocellular tumors [2]. A connection of bacteria to human neoplasms was shown for gastric MALT-lymphoma [3-5] and etiology of hepatocellular tumors [2].

The diastase resistant PAS-positive structures are compatible with intracellular bacteria. After gastric MALT-lymphoma and gastric non-cardia adenocarcinoma it appears that Hodgkin’s disease may also be a human tumor related to bacteria.

Methods

Ten PAS-stained slides of six Hodgkin patients were screened for PAS-positive intracellular structures at a magnification of × 1000 (oil immersion); at least 2400 cells in each slide were examined.

Results

PAS-positive diastase-resistant intracellular rods and spheres could be observed in Hodgkin’s disease. Figures 1-3 show the rods and the spheres. The rods are about 3 µm in length and 0.5 µm in width.

Discussion

In 1995 Christian Sauter put forward the hypothesis that Hodgkin’s disease is a human counterpart of bacterially induced crown-gall tumors in plants [10], where Agrobacterium tumefaciens is the etiologic agent [9]. In Hodgkin’s disease many features remind of a bacterial infection: Ever since the first description of Hodgkin’s disease the search for etiological agents including bacteria and fungi was intensive but unsuccessful. A viral etiology was thought more probable when Epstein-Barr virus DNA was detected in Hodgkin’s disease tissue [9].

Epidemiology

Two main epidemiological patterns are found in Hodgkin’s disease: 1. In developing countries a first peak is found in childhood, a low
incidence in the third decade, and a second peak in older adults [15].

2. In industrialized countries a low incidence is observed in children, a first peak in young adults and a second one in older adults. These epidemiological patterns may remind of a bacterial disease such as tuberculosis. Epidemiological studies by Vianna et al. [16] suggest an incubation time of years like for leprosy.

Presentation

In over 90% of Hodgkin patients the disease manifests itself in lymph nodes draining the respiratory tract [17]. With this pattern of presentation an airborne infection is quite probable.

Symptoms and laboratory findings

The fluctuating fever, chills, and night-sweats as observed in Hodgkin patients are most typical of a chronic bacterial infection. The laboratory findings (neutrophilia, increased blood sedimentation rate and elevated C-reactive protein concentrations) point in the same direction.

Histology

In contrast to “true” neoplasms there is no coherent tumor cell population. A mixture of lymphocytes, macrophages, eosinophils, plasma cells, fibroblasts, and others is found in the tissue affected by Hodgkin’s disease. Hodgkin / Reed-Sternberg cells which are believed to be the malignant cell population represent only about 0.1% to 1% [18]. The histological picture is rather compatible with a granuloma as seen in chronic bacterial infections than with “true” neoplasms.

Treatment

Hodgkin’s disease is successfully treated by radiotherapy and chemotherapy. Is this success compatible with a bacterial etiology? One thinks it is at least in early Hodgkin’s disease. Prior to the use of antibiotics localised infections were successfully treated by radiotherapy [19]. Cytotoxic drugs used in the treatment of Hodgkin’s disease show antibacterial activity [20]. The C-reactive protein (CRP) is typically elevated in bacterial infections and Hodgkin’s disease. After the implementation of a successful antibiotic treatment of a bacterial infection the CRP serum-level decreases by about 50% within 24 hours [21]. The CRP serum-concentration during the first days of a successful chemotherapy of Hodgkin’s disease shows a similar kinetic [22].

The dimensions of the intracellular rods which was observed (about 3 µm in length and 0.5 µm in width) and the diastase-resistant PAS-positivity are compatible with several groups of bacteria such as the α-2 subgroup of proteobacteria. Bartonella is related to benign human tumors including lymphomas. Agrobacterium tumefaciens belonging to the same subgroup of proteobacteria is known to induce malignant tumors in plants [9]. The PAS-positive spheres one interprets as accumulation of bacterial residues in phagosomes as in T. whipplei infections.

In conclusion it is proposed that bacteria play an etiological role in Hodgkin’s disease. We thank Regula Rüegg for photographic assistance and Elisabeth Sauter for linguistic help.
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