

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 $\times 1000$ 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 for gastric non-cardia adenocarcinoma, where *Helicobacter pylori* has been accepted as a definite biological carcinogen by the WHO / IARC [6]. Some benign human tumors are also related to bacteria such as cutaneous bacillary angiomatosis (*Bartonella*, formerly *Rochalimaea quintana*) [7], or benign lymphomas (*Bartonella henselae*) [8]. *Agrobacterium tumefaciens* is known to induce malignant tumors in plants [9]. The relationship now being established between bacteria and certain plant, animal, and human malignant tumors there is the question arising, if there are more tumors where bacteria might play an etiological role. It is proposed that the pathogenesis of Hodgkin's disease is similar to the one of crown gall tumors in plants [10], where a natural exchange of genetic material from *Agrobacterium tumefaciens* (oncogenic plasmids) to plant cells induces malignant tumors in dicotyledones [11]. The "crown gall" hypothesis for Hodgkin's disease would explain the clinical observations of a bacterial infection and the behaviour as a malignant tumor. In addition regression of Hodgkin's disease by antibiotics has been described [12].

Periodic acid-Schiff (PAS) staining is known to be an important clue to the histological identification of intracellular bacteria such as *Tropheryma whippelli* [13]. In the histological work-up of tissue of malignant lymphomas periodic acid-Schiff (PAS) stains are routinely done, but were not examined at magnifications above $\times 400$ where bacteria could be detected. Ten PAS-stained slides at a magnification of at least $\times 1000$ of six patients suffering from Hodgkin's disease were screened.

Methods

Ten PAS-stained slides of six Hodgkin patients were screened for PAS-positive intracellular structures at a magnification of $\times 1000$ (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 [14]. Epidemiological, clinical, laboratory, histological and treatment features, however, point rather to a bacterial etiology (Table 1).

Epidemiology

Two main epidemiological patterns are found in Hodgkin's disease: 1. In developing countries a first peak is found in childhood, a low

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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 lepra.

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.

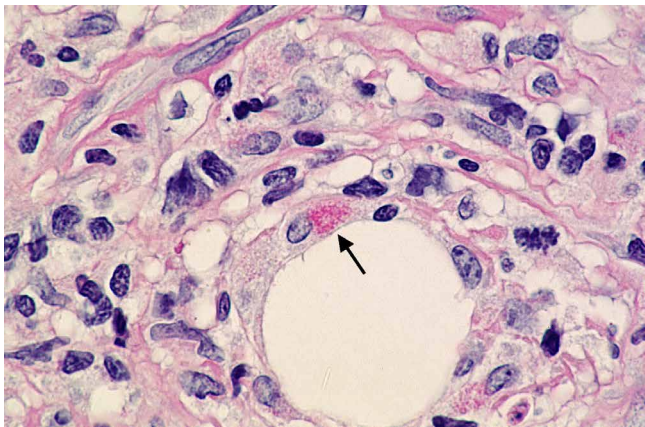


Figure 1. Intracellular rods; $\times 1000$ (arrow)

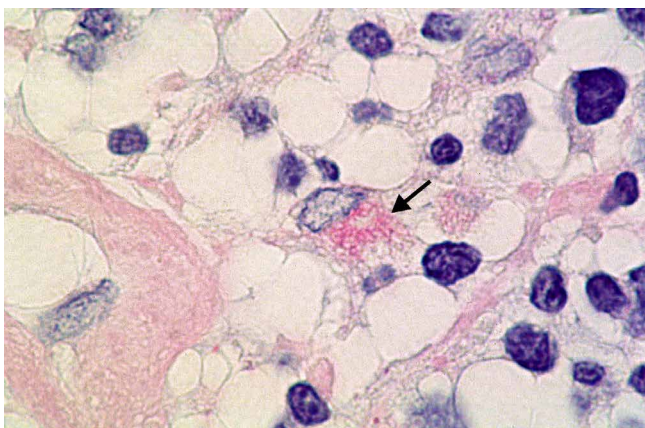


Figure 2. Intracellular rods $\times 2000$ (arrow)

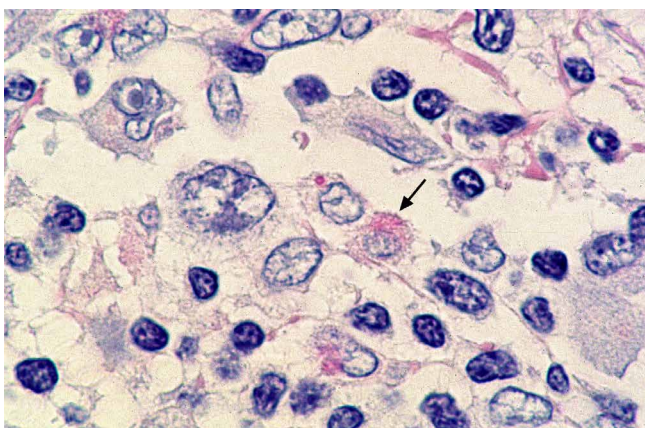


Figure 3. Intracellular rods (arrow) and sphere $\times 2000$

Table 1. Hodgkin's disease: Frequent observations pointing to a bacterial infection (+). These findings are uncommon (-) in a so called true neoplasme

| | Hodgkin's disease | True neoplasm |
|--|-------------------|---------------|
| Epidemiology | | |
| Transmission | + | - |
| Symptoms | | |
| Fever | + | - |
| Chills | + | - |
| Night sweats | + | - |
| Presentation | | |
| 130% in respiratory tract lymph nodes | + | - |
| Laboratory findings | | |
| High blood sedimentation rate | + | - |
| Elevation of C-reactive-protein (CRP) | + | - |
| Neutrophilia (with signs of bacterial infection) | + | - |
| Lymphopenia (CD 4 cells decreased) | + | - |
| Monocytosis | + | - |
| Histology | | |
| No coherent tumor cell population | + | - |

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 *Tropheryma whippelii* infections.

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

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