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Beryllium disease

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Summary: The increasing use of beryllium in a variety of industries continues to be a hazard. New cases are still being reported to the UK Beryllium Case Registry, now numbering 60 in the period 1945–1988. The majority of cases follow inhalation which results in acute beryllium disease (chemical pneumonitis) or more commonly chronic beryllium disease – a granulomatous pneumonitis. Granulomatous skin nodules also occur following local implantation. The clinical and radiological features are briefly described with the emphasis on pathology and immunology. Laser microprobe mass spectrometry analysis of tissue sections is a major advance in diagnosis. Detection of beryllium distinguishes the granulomas of chronic beryllium disease from other diseases, in particular sarcoidosis. The role of beryllium lymphocyte transformation tests is discussed. Chronic beryllium disease is steroid dependent and local excision of skin lesions appears to be curative. There is no evidence that beryllium is carcinogenic.

Introduction

Beryllium disease most commonly results from inhalation of the metal or its salts resulting in acute or chronic pulmonary beryllium disease. The other, not infrequent, route is via the skin, producing acute contact dermatitis or, in a chronic form, skin nodules and ulceration. It is of interest that though many industrial workers are potentially exposed, few develop the disease. It is considered that sensitization is an important predetermining factor.

The disease was first recognized as acute pneumonitis in Germany in 1933[1] and reached the headlines in Salem, Massachusetts with many new cases occurring in fluorescent lamp (beryllium phosphorus) workers.[2] Beryllium ceased to be used in the lamp industry in around 1951. Beryllium is a very stable, light metal (atomic weight 9), extremely hard, has good electric and thermal conductivity, is non-magnetic and is increasingly used in modern industries (Table I).

The majority of cases have been reported in North America. The USA Case Register established by Dr Harriet Hardy in Boston in 1951, now numbers over 800[3] and is continued by the National Institute for Occupational Safety and Health (NIOSH) in Cincinnati.[4] The UK Case Register[5] now numbers 60 and, though it is a rare disease, new cases continue to occur.

The criteria for the diagnosis of chronic beryllium disease are now well agreed[6]: (1) history of exposure; (2) consistent clinical and radiological features; (3) presence of granulomas; (4) the finding of beryllium in the tissues; (5) evidence of hypersensitivity.

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Table I Occupations at risk

1. Metal workers – pure beryllium, alloys, scrap metal, disposal.
2. Ceramic manufacturers – crucibles, cermats, jet engine blades, rocket covers, brake pads.
3. Electronic industry – transistors, heat sinks, X-ray windows.
4. Atomic energy industry –rocket fuels, heat shields.
5. Laboratory workers.
6. Beryllium extraction from ore.
7. Fluorescent lamp workers (ceased in 1951).

Clinical/radiological features

Though beryllium disease may affect any or all organs and is considered to be a systemic disease, the major manifestations are in the lung or skin.

Lung

Acute beryllium disease follows usually massive inhalation and is regarded as an acute toxic pneumonitis. The pathological features are those of massive oedema and non-specific reactive changes, without granulomas. The majority of patients recover but around 6% progress to chronic beryl-

lium disease.[7] Four (of 60) have been noted in the UK Case Registry.

The onset of chronic beryllium disease is usually insidious with often a long latent period of up to 20 years.[5] Patients may present with increasing dyspnoea, often weight loss, general fatigue and cough. Radiologically all lobes are affected with small granular, diffuse linear and occasionally small nodular shadowing. Pleural thickening and pneumothorax are unusual. In advance cases, the changes are those of interstitial fibrosis and honeycombing. It was originally thought that the absence of hilar adenopathy was of value in distinguishing chronic beryllium disease from sarcoidosis but both uni- and bilateral gland enlargement have been reported.[7] Physiological features are those of defective gas transfer with loss of lung compliance and sometimes airflow obstruction.

Skin

Acute contact dermatitis may result from soluble beryllium salts. Of more serious importance is the reaction to implanted beryllium metal alloy or salts sustained particularly by metal and alloy machinists and also in ceramic workers. The resulting lesion may present as a nodular scar with or without ulceration. In a recent report of 14 patients in the UK,[8] eight had lesions confined to the skin and six also had evidence of lung involvement which was most frequently associated with ulcerated skin nodules. Granulomas were present in the majority of skin nodules and were associated with the presence of beryllium and also with *in vitro* evidence of beryllium sensitivity (see below). Some skin scars however, without granulomas, also contained beryllium and without evidence of sensitization. The Mantoux and Kveim tests were negative in all those tested. To date, local excision appears to be curative but in view of a previously reported case[9] who developed widespread lymphatic nodules and 6 years later proven pulmonary disease, the outlook has to be guarded. It is recommended that patients with granulomatous skin lesons, with or without sensitization, should avoid any further beryllium exposure.

Pathological features

The microscopic hallmark of chronic beryllium disease, at any site, consists of non-necrotic epithelioid cell granulomas. These are indistinguishable from those in non-caseating tuberculosis, sarcoidosis, extrinsic allergic alveolitis and Crohn's disease.[10] The granulomas consist of closely apposed epithelioid cells closely admixed with lymphocytes and with healing, infiltrated by fibroblasts. Plasma cells and eosinophils are not a feature. Epithelioid cells frequently fuse not only to form Langhan's cells but also foreign body giant cells. Epithelioid cells are now proven to be of bone marrow derived monocytes and thus of macrophage lineage.[11] They are, however, morphologically distinguished from macrophages by showing a predominance of synthesizing rather than phagocytic cells. They show prominent Golgi complexes, are rich in rough endoplasmic reticulum and contain numerous mucoprotein-containing vesicles.[10] We suggested, at the time, that the secretory products, lymphokines and monokines, may be important in the formation and persistence of granulomas. Recent monoclonal antibody studies, on identical granulomas of sarcoidosis,[12] show that epithelioid cells lose their macrophage markers which may parallel their loss of phagocytic properties.[13] The complex interaction between epithelioid cells and lymphocytes in beryllium granulomas[14] is also similar to sarcoidosis. There is an excess of helper over suppressor T lymphocyte cells with peripheral antigen presenting dendritic cells.

Epithelioid cells may contain a variety of inclusion bodies. Schaumann bodies are concentrically laminated aggregated blackberry-like spherules consisting of calcium impregnated mucoglycoprotein often with central birefringent, possibly calcite crystals.[15] They are unfortunately not diagnostic as they are also frequent in sarcoidosis, occasionally found in tuberculosis and rarely in extrinsic allergic alveolitis.[16] Asteroid bodies, star shaped bodies and Hamazaki Wesenburg, yellowish brown granules, are also common but again are found in other granulomas. The presence of Schaumann bodies in old focal scars is, however, of value in identifying the site of previous granulomas in what might otherwise be considered to be 'idiopathic' scarring.

In the lung, the granulomas are predominantly in the interstitium and also may be related to blood vessels, bronchi and even pleura. Occasionally, the granulomas become fused, which with hyaline degeneration of collagen may form nodules up to 2 cm in diameter. Necrosis is rare but sometimes conspicuous and has been noted in both lung[17] and skin.[18] It is likely that necrosis may be associated with a high dose and/or extensive sensitization.

The prominence of alveolitis is helpful in distinguishing chronic beryllium disease from sarcoidosis and may be of more importance than granulomas as a prognostic feature indicating a poorer prognosis.[18]

Tissue analysis

Histochemical markers for beryllium have proved unsatisfactory (Denz stain), so reliance was placed

on spectroscopic analysis. With the increasing use of transbronchial, as opposed to open lung biopsy there is the serious problem of insufficient tissue available (about 30 g is required) for bulk analysis so that levels are often below the limit of detection.

Following earlier workers using laser microprobe mass spectrographic analysis,[19] it is now possible to detect beryllium in standard histological sections by direct viewing under light microscopy control (Figure 1). A 1–3 μm diameter laser beam is focused onto a granuloma and with a time of flight mass spectroscope all elements of the Periodic Table can be detected. Following an initial report,[20] beryllium has been detected in 30 cases, including both lung and skin lesions. The Laser Microprobe Mass Spectrometer (LAMMS) technique is still qualitative and though beryllium is present within the granulomas and not adjacent tissue, it cannot be detected in all of them. Control material including 25 cases of sarcoid granulomas were negative for beryllium. However, as beryllium is a natural constituent of coal, it was found in three cases of coal workers lungs. Care must therefore be taken to avoid coal dust foci in examination of suspect cases. The LAMMS technique is also useful for detecting other causes of granulomatous diseases (see below).

The finding of beryllium in urine of suspect patients is of less value than tissue analysis. In the UK series, beryllium was found in less than half the cases examined. It proves exposure and absorption but, as it may be found in healthy beryllium workers, is not proof of disease.

Immunology

Immunological factors in chronic beryllium disease have long been recognized by early workers with the development of the beryllium patch test.[21] An erythematous reaction develops 48 h after skin application of 2% beryllium sulphate solution. The test is usually, but not always, positive in diseased patients. It suffers from the disadvantage, though extremely rare, of exacerbating existing disease and certainly induces sensitivity in otherwise normal people. This has led to the development of *in vitro* tests of hypersensitivity. The beryllium lymphocyte transformation test is superior to the macrophage inhibition test and is positive in 99% of established cases.[22] It must, however, be remembered that in occasional instances detection of sensitization does not necessarily indicate the presence of disease, as

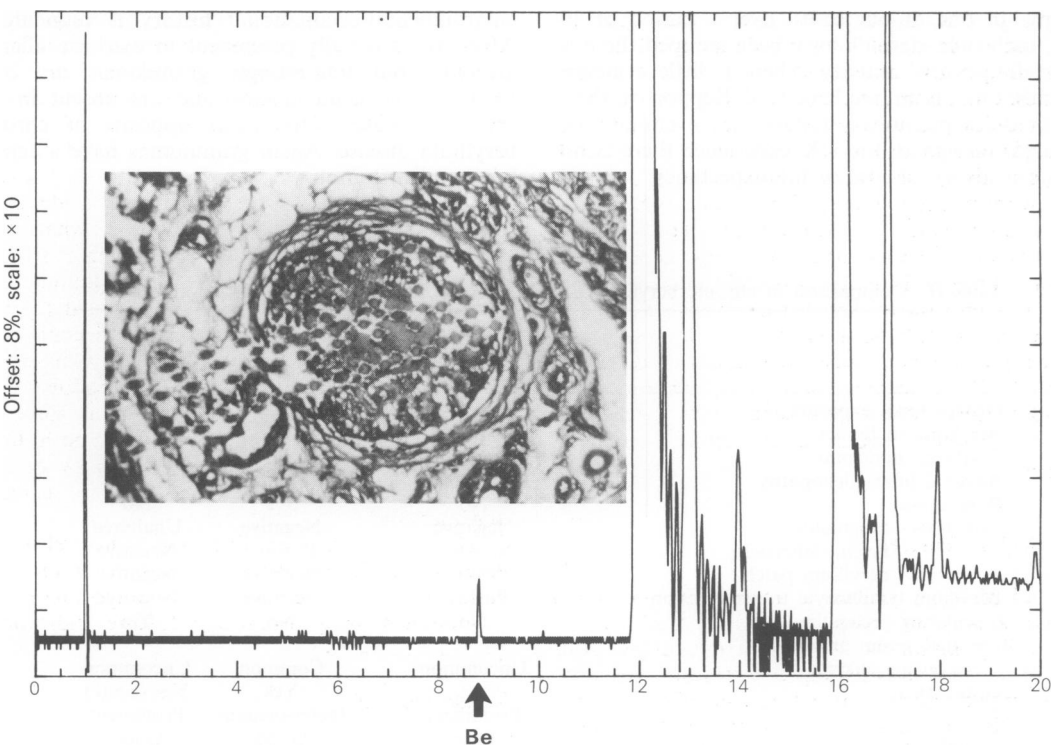

Figure 1 Laser microprobe mass spectrometer analysis of granuloma showing beryllium peak.

about 2% of otherwise normal beryllium workers give a positive result.[22]

To date in the UK series, no beryllium lymphocyte transformation test positive workers have gone on to develop chronic beryllium disease but as a proven reactive group, are kept under close surveillance. It has also been accepted that the beryllium lymphocyte transformation test be performed on first employment and repeated at annual intervals for early detection of sensitization and it also serves as an indirect test of industrial hygiene.

As in sarcoidosis, chronic beryllium disease is associated with an excess of T helper lymphocytes in bronchoalveolar lavage which may show beryllium transformation test positive though negative using peripheral blood cells.[23] These results suggest that sensitized T helper cells accumulate at the major site of involvement leaving behind inactive or even suppressor cells in the periphery.[24]

Treatment

As in so many granulomatous diseases, steroids are the main support. Usually, there is definite relief of symptoms and radiological improvement. Again, as with sarcoidosis it may mean life long maintenance therapy. In one of our cases, over a period of 30 years, each time steroids have been stopped there is a recrudescence of activity. There is little evidence that chelating agents are beneficial. Supportive therapy for cardiopulmonary failure may eventually be indicated, though in the UK experience there is no definite evidence of loss of life expectancy.

Differential diagnosis

Having briefly discussed the criteria for diagnosis it is seldom possible to satisfy each and every one, which leads to problems in the differential diagnosis[25] (Table II).

The major condition to be distinguished is sarcoidosis. It is stressed that the diagnosis is very dependent on the occupational history and on the finding of beryllium in the granulomas, supported by evidence of sensitization. The clinicoradiological features are not always diagnostic. Chronic beryllium disease patients, however, tend to have a history of weight loss with more severe complaints of generalized ill health. Though the granulomas are similar in both diseases, the predominantly small airways centrilobular distribution in chronic beryllium disease is helpful as is the well marked alveolitis. A recent case illustrates the difficulties. One of our patients satisfied all the criteria, except for a strongly positive Kveim test – he may well suffer from both diseases as the Kveim test in the USA and UK series is negative. Raised serum angiotensin converting enzyme levels, though frequent in sarcoidosis, may also occur in chronic beryllium disease.

The other close mimic of chronic beryllium disease is extrinsic allergic alveolitis.[26] Again a proper environmental/occupational history is mandatory. Alveolitis is equally prominent in extrinsic allergic alveolitis but interestingly granulomas are only found in the acute disease and are absent in the chronic disease – the exact opposite of chronic beryllium disease. Again granulomas have a centrilobular distribution.

Table II Comparison of chronic beryllium disease, sarcoidosis and extrinsic allergic alveolitis

	Chronic beryllium disease	*Sarcoidosis*	*Extrinsic allergic alveolitis*
Occupational exposure	Yes	No	Yes
Beryllium in tissues	Yes	No	No
Erythema nodosum	No	Yes	No
Bilateral hilar/adenopathy	Uncommon	Common	No
Bone cysts	No	3%	No
Skin tests:- tuberculin	Negative	Negative	Unaltered
Kveim/Siltzbach	Negative	Positive	Negative
beryllium patch	Positive	Negative	Negative
Beryllium lymphocyte transformation	Positive	Negative	Negative
Circulating precipitins	No	No	Yes
Elevated serum angiotensin converting enzyme	Uncommon	Common	Uncommon
Granulomas	Yes	Yes	Yes (acute)
Alveolitis	Prominent	Inconspicuous	Prominent
Prognosis	Poor	Good	Good

Necrotizing sarcoidal granulomatosis[27] must also be considered. Though the granulomas may be similar, necrosis is usually marked. A major distinction is the prominent vasculitis with resulting haemoptysis. The disease is of unknown cause and beryllium has not been detected.

Other metal-induced hypersensitivity diseases, such as aluminium[28] and titanium[29] though very rare, may cause confusion. They can be distinguished by obtaining a careful occupational history, testing for skin sensitivity and using the laser microprobe mass spectrometer technique to identify the metal within the granulomas.

In all cases of granulomatous lung disease, care must be taken to exclude infective agents, chief of which is *M. tuberculosis*. Industrial workers are not immune and in some work places may even be at greater risk. In some areas of the world, such as Ohio, histoplasmosis may be a close mimic, the fungus may be very sparse and difficult to demonstrate and cases do occur even in the UK.[30]

A brief word about the carcinogenicity of beryllium. Though there is experimental evidence,[31] in man it is inconclusive. We have no reported cases of lung cancer in the UK. There is, however, some disputed evidence from the USA[32] but the beryllium Queen, Dr Harriet Hardy,[33] remains unconvinced.

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