**CASE REPORT**

**Bronchocentric granulomatosis and central diabetes insipidus successfully treated with corticosteroids**

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**ABSTRACT:** Bronchocentric granulomatosis (BCG) is a rare chronic granulomatous lung disease that leads to destruction of the airway walls. It has been observed in association with various conditions, but never, so far, been reported to involve the central nervous system.

We report a case of histologically confirmed pulmonary bronchocentric granulomatosis temporally associated with a partial central diabetes insipidus (CDI).

Although the pathological basis of the posterior pituitary gland involvement was not ascertained, the temporal association of bronchocentric granulomatosis and central diabetes insipidus, as well as the fact that corticosteroid treatment provided stable remission of both conditions after a 10 month follow-up, strongly suggest that central diabetes insipidus was aetiologically related to bronchocentric granulomatosis in this patient.


Bronchocentric granulomatosis (BCG) is a rare necrotizing granulomatosis that is usually confined to the lung. After the first report of this disease by LIEBOW [1] in 1973, BCG was described in greater detail and recognized as a distinct entity from allergic bronchopulmonary aspergillosis, eosinophilic pneumonia, mucoid impaction of bronchi, microgranulomatous hypersensitivity reactions (extrinsic allergic alveolitis) and Wegener's granulomatosis [2–5]. BCG has since been diagnosed with increasing frequency, and at least 72 cases have been reported so far in the literature [6–28].

Unlike Wegener's granulomatosis, BCG primarily involves the airway wall and leads to its destruction [2, 29]. Interestingly, BCG has been described in association with pulmonary cavitation, asthma and aspergillosis [6–18], pulmonary echinococcosis [19], Wegener's granulomatosis [20], rheumatoid arthritis [10], ankylosing spondylitis [12], glomerulonephritis [13], scleritis [21], and polyarthritis [14]. Whilst involvement of the central nervous system has often been observed in Wegener's granulomatosis [4, 5], it has never been described in BCG. Eight cases of CDI have been reported in Wegener's granulomatosis [5, 30–32]; whereas, to the best of our knowledge, none has ever been described in BCG.

We recently observed a patient with BCG, who presented with paranasal sinus involvement and multiple lung masses, which were followed by the onset of CDI, and in whom both the pulmonary lesions and the CDI were successfully treated with prednisone.

Case report

A 55 year old woman was referred to us because of low-grade fever, malaise and dry cough. She was first seen at another hospital in August 1990 because of left hypoacusia, vertigo, nausea, and nystagmus, which were attributed to acute labyrinthitis. The patient was then referred to an Otolaryngology department because of recurrence of these symptoms and the onset of malaise and headache, nausea and vomiting. In October 1990, acute mastoiditis was diagnosed and a mastoidectomy, which was followed by partial relief, was carried out. However, a month later, she was operated on at her nasal concha because of "chronic sinusitis". No result of histological evaluation was available at that time. The patient was, thereafter, in good health until February 1991, when she started complaining of malaise, low-grade fever (37.2–37.3°C) and cough. As a chest X-ray showed a right middle lobe opacity, she was admitted to another hospital. Based on a bronchoscopic examination, "chronic bronchitis" was diagnosed; whereas, repeated cytological examinations of her bronchial brushing showed no neoplastic cells or infectious agents. She was then discharged, but soon readmitted to the same hospital because of persistence of malaise and fever. On chest X-ray, an anterior opacity at the right lower lobe was noticed. A computed tomographic (CT) scan of the lungs showed a small atelectatic wedge-shaped band with apex at the right inferior hilar horn. A repeated bronchoscopic examination suggested chronic hypertrophic...
haemorrhagic bronchitis. The patient was then discharged with a diagnosis of middle lobe syndrome, and treated with antibiotics and deflazacort (30 mg·day⁻¹ for 4 days, with tapering of the dosage over a two week period) with partial remission.

In October 1991, the patient started experiencing polyuria and polydipsia with a daily water intake of 7–8 l. She was readmitted to the same hospital, and a measurement of anti-diuretic hormone revealed a baseline level of 2.2 ng·l⁻¹, below the normal range (4–12 ng·l⁻¹), but no dehydration test was performed. A skull X-ray and a CT scan of the brain did not show any sellar enlargement. As a spontaneous partial remission of the polyuria and polydipsia occurred on a daily water intake of 3–4 l, the patient was discharged without treatment. However, over the following year, she kept complaining of dry cough, malaise and low-grade fever, and her erythrocyte sedimentation rate (ESR) remained persistently above 100 mm. Therefore, in November 1992 she was referred to our clinic. On admission, the physical examination was normal; there was low-grade fever (37.5°C); the white blood cell count showed 9×10⁹·l⁻¹ with a normal differential, and the ESR was 102 mm. A few red blood cells were found at urinalysis, and an Addis count showed 4,200,000 per 12 h (normal values <500,000 per 12 h), but normal blood urea nitrogen (BUN) and serum creatinine were found. The antineutrophil cytoplasmic antigen antibody [33] and the immunoglobulin E (IgE) against Aspergillus fumigatus were both undetectable. The patient had neither a family history of diabetes insipidus nor a history of asthma, peripheral eosinophilia, previous global cerebral ischaemia, head trauma or drug/medication use. A 14 h water deprivation test [34] (table 1; 7/11/92), was stopped because one of its end-points, i.e., an increase of the urine osmolality by less than 30 mOsm·kg⁻¹ in three consecutive samples, was attained. The test demonstrated an impaired capacity of urine concentration, and confirmed the deficit of ADH secretion (table 1). A magnetic resonance imaging (MRI) scan of the brain showed no focal lesions either in the posterior pituitary gland or in the hypothalamus, but a hypotrophic post-pituitary gland (fig. 1). Normal plasma prolactin, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH) levels and postmenopausal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were found.

A first chest X-ray was judged to be normal, whereas, at a second examination, a slight opacity at the right lobe base was noticed. A lung CT scan disclosed the presence of five solid masses, ranging 1–5 cm in diameter. One was located at the apex of the lower left lobe and surrounded the segmental bronchus, causing some narrowing (fig. 2a arrows); of the other four masses, which were located at the pulmonary bases, one was found at the lingula (fig. 2a arrow). Repeated bronchoscopic examinations visually confirmed the previous finding of chronic hypertrophic haemorrhagic bronchitis; however, because of the risk of bleeding, a biopsy was not undertaken. A first attempt to perform a CT-guided transthoracic fine needle biopsy was unsuccessful. A second transthoracic fine needle biopsy with extemporaneous cytological examination was eventually performed one month later (fig. 2b). This allowed detection of inflammatory cells and ruled out the neoplastic nature of the mass.

In March 1993, the patient underwent an open lung biopsy. Histological examination of the mass was consistent with a diagnosis of BCG (fig. 3a–c).

Table 1. – Results of the dehydration tests

<table>
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<tr>
<th>Date of test</th>
<th>Urine osmolality mOsm·kg⁻¹</th>
<th>Plasma osmolality mOsm·kg⁻¹</th>
<th>ADH ng·l⁻¹</th>
<th>Urinary cAMP nmol·l⁻¹</th>
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<td>NP</td>
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<td>&lt;1</td>
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<td>557</td>
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<td>306</td>
<td>1.4</td>
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</table>

*: after one month of prednisone treatment. NP: not performed; Basal: baseline; DDAVP: deamino-D-arginine vasopressin; ADH: anti-diuretic hormone; cAMP: cyclic adenosine monophosphate.

Fig. 1. – T₁-weighted magnetic resonance imaging (MRI) examination of the hypothalamic and pituitary regions demonstrated no masses in the hypothalamic region and absence of hyperintense signal in correspondence to the posterior pituitary gland, suggesting hypoatrophia, possibly due to a stalk damage (arrow).
Fig. 2. – a) Twenty eight months after the clinical onset, the first computed tomographic (CT) examination of the lungs revealed the presence of a solid mass surrounding the apical bronchus of the lower left lobe, in the costovertebral space, near the descending thoracic aorta (3 arrows). Another four masses were present at the basal segments of both lungs, one of which is evident in this section at the lingula (single arrow). b) The same CT section through the lungs two months later. Spontaneous, partial regression of the costovertebral mass is evident (arrows), but concomitant enlargement of the lingular mass is also evident. Note also the fine needle biopsy in the lingular mass, which revealed an inflammatory infiltrate. c) The same CT section through the lungs 2 months after an open chest biopsy had allowed a diagnosis of bronchocentric granulomatosis and after one month of full-dose prednison treatment. Almost complete regression of both the costovertebral and the lingular masses is evident. Only some thickened structures at the lingula and the para-aortic space are still evident (arrows). The lesions at the basal lung regions (not in the picture) had completely disappeared. Note also the abundant mediastinal fat tissue, most probably a consequence of the steroid assumption.

Fig. 3. – a) Bronchiolar wall is infiltrated by a mixture of histiocytes, lymphocytes, and granulocytes that dissociate the mucosae from the cartilaginous tissue (on the left). (Scale bar=150 nm; haematoxylin and eosin stain). b) With the use of anti-cytokeratins monoclonal antibody, the bronchocentric distribution of the inflammatory infiltrate is evident, with the clear delineation of the epithelial structures (bronchiolar epithelium in the centre, and alveolar epithelium at the bottom). (Scale bar=150 nm; anti-cytokeratins, avidin biotin (immunoperoxidase) complex). c) A cross-section of an arterial wall adjacent to the granulomatous lesions. It is possible to see the normal conformation of the vessel. (Scale bar=200 nm; van Gieson's elastin stain).
by complete remission of cough, fever and malaise, by normalization of ESR and by a decrease of daily water intake (from an average of 4.0 to 2.0 l). A CT scan performed after 1 month of treatment showed a marked decrease both of size and density of the lung masses previously observed (fig. 2c). Repeated ANCA and Aspergillus fumigatus specific antibodies were negative. A third dehydration test, demonstrated an increase of ADH levels, which for the first time became detectable with our method, although the levels relative to plasma osmolality were still consistent with a diagnosis of partial CDI [35]. In addition, evidence of a restored normal renal responsiveness to both endogenous and synthetic ADH, as shown by the increase of cyclic adenosine monophosphate (cAMP) urine excretion (table 1; 2/6/93), was attained.

After 10 months of follow-up, whilst on a maintenance dosage of 0.25 mg·kg⁻¹ body weight deflazacort, calcium lactate 2.9 g·day⁻¹ calcium carbonate 0.3 g·day⁻¹ and calcifediol 100 µg·day⁻¹, the patient is in good health, afibrile, and her ESR has remained consistently normal. Furthermore, her daily water intake is consistently between 2 and 2.5 l.

Histological findings

Microscopically, the lesions consisted of granulomatous areas with multiple foci of necrosis surrounded by palisaded histiocytes and occasional giant cells. Necrotizing vasculitis was not present and vascular walls were substantially preserved, and showed only an inconspicuous number of lymphocytes and plasma cells (fig. 3c). On the contrary, bronchiolar structures were heavily dissociated by histiocytes, lymphocytes and granulocytes (fig. 3a and b). In some areas the parenchymal architecture was completely obscured by inflammation and necrosis. The elastin staining, which is mandatory in order to demonstrate the bronchocentric rather than angiocentric origin of the granulomatous disease, showed the normal conformation of the arterial wall; thereby, confirming the diagnosis of BCG (fig 3c).

Discussion

BCG is a rare idiopathic granulomatous necrotizing disease of the airways, usually confined to the lungs. In 30–40% of cases it occurs in patients with chronic asthma and particularly in those with aggressive bronchopulmonary aspergillosis, but in the majority of the patients there is no evidence of atopy [2, 29]. It is usually diagnosed at histological examination of an open lung biopsy and is curable with corticosteroids. Unlike Wegener's granulomatosis, BCG was deemed to be confined to the lungs, although it has occasionally been reported to be associated with glomerulonephritis [13], and scleritis [21]. However, BCG has never been reported to involve the central nervous system. We report a case of partial central diabetes insipidus, temporally associated with histologically documented BCG. The central site of the ADH deficit was demonstrated by the undetectable baseline ADH levels, as well as by the lack of any detectable rise in ADH in response to two different dehydration tests (table 1). Since, in addition, an impaired renal response to the synthetic analogue of ADH, DDAVP, was observed at the second test (table 1; 30/4/93) and no urine cAMP measurement was available at that time, we could not conclusively rule out the additional possibility of some renal resistance to ADH. However, an inconclusive renal response to DDAVP has already been observed in partial central diabetes insipidus, for reasons which are unclear [34]. Furthermore, the fact that only mild microhaematuria and no other sign of renal involvement was evident in this case, as well as the finding of a normal renal response to a repeated dehydration test and to DDAVP, made the possibility of a nephrogenic diabetes insipidus unlikely.

It might be argued that the clinical course of this patient could also be consistent with Wegener's granulomatosis, and indeed a bronchocentric Wegener's granulomatosis has been described [20]. Furthermore, the current literature emphasizes the common extrapulmonary involvement in Wegener's granulomatosis [29]. Such involvement has been reported only occasionally in BCG [13, 21, 28]. However, the pulmonary histological findings conclusively showed the bronchocentric origin of the inflammatory process without vasculitis in our patient (fig. 3).

Since both BCG and central diabetes insipidus are rare diseases, the conditional probability that they concur by chance in the same patient would be, according to Bayes' equation, exceedingly low. It has to be acknowledged that the aetiology of the central diabetes insipidus in this patient remains undetermined, since no histological examination of the hypothalamic-pituitary region was affordable and no evidence of lesions was found, both at CT scan and at MRI of the hypothalamus and the posterior pituitary gland. However, the typical T₁-weighted hyperintense signal of the posterior pituitary gland was scantily discernible at MRI (fig. 1), a finding that suggested hypothroaphy of the gland. Only in one of the three cases of central diabetes insipidus associated with Wegener's granulomatosis, histologically assessed postmortem, was evidence of granulomatous involvement of the pituitary gland found. Accordingly, the following pathogenic mechanisms have been hypothesized to explain development of central diabetes insipidus in those patients: a) vasculitis of the posterior and/or anterior pituitary gland and/or the hypothalamic blood vessels, causing arterial lumen narrowing and, thereby, an ischaemic stalk damage with ensuing atrophy of the gland; b) necrotizing granulomata spreading from the nasal or paranasal structure to the base and causing direct damage to the supraoptic and/or paraventricular nuclei in the absence of pituitary enlargement; and c) in situ granuloma formation in the posterior and/or anterior pituitary gland leading to compression of the tissue and subsequent hormone failure [30]. Since our patient had no radiological or hormonal evidence of anterior pituitary enlargement, but exhibited a hypotrophic posterior pituitary gland, the first explanation, i.e. a direct posterior gland damage due to a vasculitic involvement of the hypothalamic nuclei
and the stalk, could be advanced. However, no evidence of vascular lesions was found in the lung. Furthermore, damage to the tract below the median eminence or removal of the posterior pituitary only produces a transient period of diabetes insipidus. At variance, a chronic deficit of ADH secretion was observed in this case, suggesting a BCG involvement of the region of ADH elaboration above the median eminence, i.e. the hypothalamic nuclei, by either necrotizing granulomas or vasculitic damage. None of these events seem to have induced detectable radiological evidence of hypothalamic damage in our patient, even at MRI.

A further consideration can support an aetiologic role for BCG in this case of partial central diabetes insipidus. It is well-known that steroids inhibit ADH secretion, and may, thereby, cause a worsening of polyuria and polydipsia in patients with central diabetes insipidus. In contrast, in our patient, a prompt and clear-cut improvement both of daily water intake and of the ADH response to a repeated dehydration test was observed concomitantly with an impressive regression of the pulmonary masses (fig. 2).

In conclusion, we believe that the partial central diabetes insipidus and the pulmonary BCG observed in this case were not simply a casual co-existence of two rare unrelated diseases, but rather the first example of BCG involvement in the central nervous system and causing central diabetes insipidus. The fact that both conditions were successfully treated with corticosteroids lends support to this interpretation.

References

31. Haynes BF, Fauci AS. Diabetes insipidus associated with Wegener’s granulomatosis successfully treated...