Tracheal enlargement or Mounier-Kuhn syndrome in giant cell arteritis: a possible causal association with therapeutic implications

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Abstract

Giant cell arteritis (GCA) is a large-vessel vasculitis with rarely described respiratory initial manifestations. We report such a case presenting with hoarseness, stridor, cough and dyspnea, in which a tracheomegaly with tracheomalacia was found. No signs of relapsing polychondritis were present. The respiratory symptoms rapidly improved after glucocorticoids and Azathioprine. Tracheomegaly or Mounier-Kuhn syndrome is characterized by marked dilatation of trachea and central bronchi. The differential diagnosis and the possible relationship between tracheomegaly and GCA involving metalloproteinase-induced elastolysis are discussed. This is the first case, to our knowledge, of Mounier-Kuhn syndrome in vasculitis. The association of tracheomegaly with GCA may be underestimated, as the diagnosis is not always obvious on conventional radiographs. A tracheal enlargement finding in GCA requires monitoring to ensure early detection and prevention of spontaneous tracheal rupture. Adding a metalloproteinase inhibitor like Doxycycline to GCA therapy would be rational for the prophylaxis of complications.

Keywords: tracheomegaly, Mounier-Kuhn syndrome, giant cell arteritis, vasculitis, metalloproteinase, aneurysm.

Introduction

Tracheomegaly or Mounier-Kuhn syndrome (MKS) (also called tracheobronchomegaly, tracheal diverticulosis, or tracheocele) is a chronic, inherited or acquired disease characterized by marked dilatation of trachea and central bronchi, related to the atrophy of elastic fibers and smooth muscle [1, 2]. In the definition of tracheomegaly, sometimes the tracheal enlargement overlaps with the terms of tracheomalacia, tracheobronchomalacia and tracheobronchopathia malacia that describe the respiratory structures collapse during breathing [2]. The disease is usually diagnosed in adult males, in the third or fourth decade of life [1].

Tracheomegaly was first described in 1897 by Czyhlarz and characterized in 1932 by Mounier-Kuhn [3, 4]. Less than 400 cases have been described ever since [5]. Nevertheless, MKS may be not as uncommon as tracheomegaly was reported in up to 16.6% of chest CTs in patients with bronchiectasia [2, 4]. The real prevalence of MKS is unknown, as it is not always symptomatic and apparent on routine chest radiographic screening [6]. The hallmark of MKS is the important dilatation of the trachea (over 3 cm) and central bronchi (over 2.4 cm right, 2.3 cm left respectively) with normal peripheral airways [1, 7].

The clinical manifestations range from frequent respiratory tract infections, sometimes with large amount of purulent sputum production, occasional hemoptysis and progressive respiratory insufficiency, to minimal or no symptoms in some patients [6]. On conventional X-ray tracheomegaly may be overlooked [6], although an irregular, corrugated air column may be found, resulting from redundant mucosal folds between the tracheal rings [1]. During radiological examination, the tracheal size increases with Valsalva and narrows with Müller’s maneuver [7]. Functional tests may detect increased tidal volume, total lung capacity and dead spaces and decreased bronchial flow speed, obstructive pathology or may be normal [8, 9]. Bronchoscopy may confirm dynamic airway collapse and diverticula [8]. Giant cell arteritis (GCA) is the most common large-vessel vasculitis. GCA may rarely manifest with respiratory symptoms. Cough in GCA, sometimes the presenting feature, usually occurs due to inflammation of various respiratory tree structures, and rarely due to aortic aneurysms compressing the trachea or great bronchi [10].

We describe a patient with a late diagnosis of tracheomegaly, of uncertain onset, in whom the persistent cough led to the diagnosis of GCA.

Case presentation

A 73-year-old, Caucasian male patient presented for dyspnea, dry cough, hoarseness, stridor and a 4 kg weight loss, not influenced by antibiotic therapy (Ciprofloxacin, followed by Amoxicillin–Clavulanate). He was living in the countryside and had been formerly a mayoral clerk,
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The patient was non-smoker, but had smoked for two years in his youth from the age of 23 to 25, about five cigarettes/day. He had no chronic cough and reportedly was previously healthy, apart from a villonodular synovitis of the third left finger operated at the age of 65. His familial history included only arterial hypertension in both parents.

The cardiology consultation with electrocardiography and echocardiography identified minor ischemic changes, but ruled out cardiac asthma. The chest X-ray and computed tomography (CT) revealed tracheomegaly (3.7 cm diameter), with a right posterior lateral wall diverticulum (Figures 1 and 2) and increased caliber of the great bronchi (2.2 cm right, 2.5 cm left). No previous chest radiographs or CTs were available, but the written conclusions of medical routine controls including chest radiography at the ages of 18, 61 and 65, respectively, had been normal. The fibrobronchoscopy revealed tracheomalacia with dynamic partial stenosis upon expiration. The laboratory tests showed inflammation [erythrocyte sedimentation rate (ESR) 52 mm/h (normal values 5–30 mm/h) and C-reactive protein (CRP) 12 mg/L (normal values 0–6 mg/L)]. The nasal and pharyngeal swabs, blood cultures, IgM for Mycoplasma and Chlamydia (enzyme-linked immunosorbent assay – ELISA) were negative, as well as the sputum examination with Ziehl–Neelsen staining and the intradermoreaction for tuberculosis. The patient received N-Acetylcysteine (600 mg/day) and Erdosteine (600 mg/day), associated with probiotic therapy, but the cough was only minimally influenced.

One month afterwards the patient presented to the rheumatologist for a sleep-interfering cervical pain. The physical examination revealed no significant cervical contracture, movement limitation or tender Arnold points, but instead left temporal artery sensitivity, stridor and rare rhonchi were found. No carotideal or other bruits were detected, and the arterial pressure in the hands was equal (135/60 mmHg). He had no digital clubbing. Apart from increased inflammatory markers (ESR 105 mm/h, CRP 24 mg/dL), all other laboratory test, including the screening for hepatitis B and C, human immunodeficiency virus (HIV) tests, alpha-1 antitrypsin, immunoglobulins, antinuclear and anti-neutrophil cytoplasm antibodies and complement fractions were normal.

The histopathological examination of the biopsy sample taken from the left superficial temporal artery with Hematoxylin–Eosin (HE) staining and Orcein staining for elastin, revealed intimal thickening, fragmentation of the internal elastic lamina and mononuclear cell infiltrate with media invasion and giant cell formation in the vessel wall specimen, suggestive of GCA (Figures 3 and 4).

Figure 1 – Thoracic CT, pulmonary window, showing tracheomegaly (marked transversal tracheal dilatation). CT: Computed tomography.

Figure 2 – Thoracic CT, pulmonary window, coronary MPR, depicting tracheomegaly (marked dilatation of trachea and bronchi). CT: Computed tomography; MPR: Multiplanar reconstruction.

Figure 3 – Superficial temporal artery specimen, cross-section showing intimal thickening (HE staining, ×60).

Figure 4 – Image of the artery wall, in which the mononuclear cell intimate infiltration is noted (HE staining, ×100).
An angio-magnetic resonance imaging (MRI) of the aortic cross and branches did not show thoracic aortic aneurysms or inflammation of the main vessels examined. A thorough history and clinical examination ruled out inherited connective tissue disorders or relapsing polychondritis as possible causes for tracheal enlargement. High-dose glucocorticoids (one 250 mg Methylprednisolone pulse followed by Prednisone 60 mg/day with tapering) and Azathioprine (2.5 mg/body weight) resulted in rapid improvement with disappearance of cough and stridor. At the six months control, he was asymptomatic on Azathioprine 150 mg/day, low-dose Prednisone (7.5 mg/day), along with position physiotherapy, Acetylcysteine (600 mg/day) and Doxycycline courses (200 mg/day, 10 days/month).

**Discussions**

Tracheomegaly or MKS is the consequence of elastic fibers and smooth muscle atrophy in the trachea and main bronchi. A congenital connective tissue weakness, in combination with inhalation of irritants like air pollution and cigarette smoking, are incriminated as possible factors [3]. Inherited tracheal enlargement is secondary to connective and/or smooth muscle tissue dysplasias, such as Ehlers–Danlos syndrome, Marfan syndrome or cutis laxa, while the acquired form results from inflammation and elastolysis, or tracheal traction by upper lobe fibrosis [6, 11]. Tracheal enlargement may also be seen in chronic obstructive pulmonary disease, with increase of sagittal and reducing of coronal diameters (“saber-sheath trachea”) [1, 6]. In relapsing polychondritis, the tracheal enlargement from cartilaginous structures alteration typically spares the posterior tracheal membrane [1, 6]. On the contrary, in MKS the atrophy or reduction of the elastic fibers in the posterior tracheal membrane likely contribute to the tracheal collapse during inspiration [12].

An anatomic classification describes three MKS types: type 1, with slight symmetric dilatation of trachea and main bronchi, type 2, with distinct tracheal dilatation and diverticuli, and type 3 with diverticular and saccular structures that extend to the distal bronchi [8].

A clinical classification, based upon an extensive review of 365 cases of MKS, identifies the main etiological types. The disease developed in type 1A after fetoscopic tracheal occlusion and in type 1B after prolonged intubation in infants and children. In type 2, the disease occurred after recurrent pulmonary infections (type 2A), or pulmonary fibrosis (type 2B). Type 3 is associated with extra-pulmonary elastolysis (18 patients), and in type 4 no clear predisposing factors are found [5].

The gross pathology in MKS reveals dilatation of the trachea and main bronchi, with rapid change to normal caliber at the fourth and fifth-order airways [7]. The mucosal herniation between the cartilage rings results in airway outpouchings or diverticuli, which may harbor pooled secretions. The microscopy shows atrophy or absence of elastic fibers, and thinning of the muscularis mucosa, atrophy of the longitudinal smooth muscles of the trachea and central bronchi, and sometimes the absence of the myenteric plexus of the airways [6].

In our patient, the etiology of tracheomegaly and its onset are unclear. However, he had no familial and personal history of connective tissue diseases or chronic obstructive pulmonary disease, nor professional toxic exposure. Although he had not been smoking for 50 years, smoking could not be ruled out for sure, but was unlikely. It is possible that he had an asymptomatic and hence underdiagnosed MKS for many years, or that he developed the tracheomegaly later in life.

While some MKS cases are congenital, there is evidence accumulating in favor of an acquired etiology. Histopathological findings of localized airway smooth muscle degeneration and remodeling have been recently reported in MKS [13, 14]. In these cases, airway smooth muscles are present, and not congenitally absent, and there are regional alterations of airway smooth muscles with degeneration and fibrotic remodeling, as opposed to atrophic loss [11]. In autoimmune diseases, tracheomegaly was described in rheumatoid arthritis [15, 16], in ankylosing spondylitis [17], juvenile idiopathic arthritis and scleroderma [18]. We are not aware of other reports of tracheomegaly in vasculitis.

Tracheal vasculitis is usually associated with granulomatosis with polyangiitis and rarely with Churg–Strauss syndrome. GCA is a large-vessel vasculitis with rarely described respiratory presentation. Any segment can be involved, from respiratory airways to lung parenchyma, pleura or pulmonary vessels (Table 1).

### Table 1 – Respiratory involvement in giant cell arteritis

<table>
<thead>
<tr>
<th>Type of involvement</th>
<th>References</th>
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<tr>
<td>Bronchitis</td>
<td>Siuko &amp; Vaara, 1968 [19]; Currie et al., 2008 [20]</td>
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<tr>
<td>Bronchiolitis</td>
<td>Roddy et al., 2006 [21]</td>
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<tr>
<td>Interstitial lung disease</td>
<td>Karam &amp; Fulmer, 1982 [22]; Kramer et al., 1998 [23]; Clarke et al., 1995 [24]; Carassou et al., 2010 [25]</td>
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<tr>
<td>Nodules</td>
<td>Bradley et al., 1984 [26]; Kramer et al., 1998 [23]; Zenone et al., 1994 [27]; Carassou et al., 2010 [25]</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>Romero et al., 1992 [28]; Gur et al., 1996 [29]; Colnot, 1996 [30]; Valstar et al., 2003 [31]; Kechaou et al., 2008 [32]</td>
</tr>
<tr>
<td>Pulmonary arthritis</td>
<td>Wagenaar et al., 1981 [33]; Glover et al., 1987 [34]; Doyle et al., 1988 [35]; Feng et al., 2004 [36]</td>
</tr>
<tr>
<td>Pulmonary thromboembolism</td>
<td>Radhananohar, 1991 [37]; Chassagne et al., 1995 [38]; Beynel et al., 1997 [39]; Landrin et al., 1997 [40]; Andrès et al., 2004 [41]</td>
</tr>
<tr>
<td>Aortic aneurysm complicating the trachea or bronchi</td>
<td>Dennison et al., 1985 [42]</td>
</tr>
<tr>
<td>Alveolar hemorrhage</td>
<td>Garrous et al., 2008 [43]</td>
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In our case, the angio-MRI failed to demonstrate inflammation of the tracheal arterial supply or the presence of aortic aneurysms. Nevertheless, tracheal involvement in GCA may be infrequent; spontaneous tracheal rupture during cough was reported in a longstanding case [44]. Glucocorticoids, as frequently required in vasculitis, were also incriminated in tracheal rupture [44].

A potential link between MKS and GCA may concern elastin damage by matrix metalloproteinases (MMPs), involved in vascular inflammation and tissue remodeling [44]. In support of this hypothesis, a recent report in a patient with lung transplantation for MKS revealed no
genetic alterations in the explanted bronchi, but diffuse inflammation with strong reduction in the elastic fibers and increased expression of MMP-1, -2 and -9 [14]. The human tracheal smooth muscle cells, critically involved in remodeling, express MMP-9 during inflammation that contributes to extracellular matrix degradation [45]. Of note, extra-pulmonary elastolysis was involved in almost 5% of MKS cases, in a recent extensive review [5]. Moreover, a MKS patient with elastolysis also had a mildly dilated aortic root [5].

In GCA, the balance between MMP and their natural inhibitors-tissue inhibitors of metalloproteinases (TIMPs), favors proteolytic activity, and elevated MMP-2 and MMP-9 contribute to aneurysm formation through facilitating leukocyte access across the vessel wall and rupture of internal elastic lamina [46]. Moreover, the elastin degraded by MMP-secreting macrophages triggers an immune response [46]. Therefore, a similar inflammatory etiology of tracheomegaly in GCA, although speculative, is not unlikely.

Our patient did not have concomitant thoracic aortic aneurysms. Possible explanations could be the regional variations in matrix structure or MMPs regulation, or other factors related to immune and/or vascular aging. Although an asymptomatic prior tracheal enlargement cannot be ruled out, the sudden and late respiratory symptoms point to an acquired etiology, presumably inflammatory in GCA. The rapid resolution of cough and dyspnea was most likely due to reversible inflammation of the smaller bronchial vessels.

Therapy in tracheomegaly consists in position physiotherapy for clearing secretions, antibiotics and rarely airway stenting and tracheoplasty [6]. Moreover, MMP inhibition, for instance with Doxycycline, a non-specific proteinase inhibitor, along with antibacterial effects, may limit the aortic and airway remodeling [47–49].

Conclusions

The association of tracheomegaly with GCA may be underestimated, as tracheal enlargement is not always obvious on conventional radiographs. A tracheal enlargement in GCA requires monitoring for early detection of a spontaneous tracheal rupture, mainly in the setting of long-term glucocorticoids. Supplemeting the GCA treatment with a metalloproteinase inhibitor like Doxycycline could prove rational for the prophylaxis of complications.

Conflict of interests

The authors declare that they have no conflict of interests.

Declaration of patient consent

The authors certify that the patient has given the informed consent for publication of clinical information, including that of images, with efforts to preserve his anonymity.

References


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Received: January 8, 2018
Accepted: August 29, 2018