

# Silicosis and renal disease: insights from a case of IgA nephropathy

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**Abstract:** A 68-yr-old male, smoker, is admitted for proteinuria (2,800 mg/24 h) and reduced renal function (serum creatinine 2 mg/dl, GFR 35 ml/min). Renter, he started working 20-yr-old as a sandstone cave miner. Despite the high levels of silica dusts, he reported no mandatory use of airways protection devices during the first 25 yr of activity. No clinical or radiological signs of silicosis or pneumoconiosis were reported until the year of retirement (1997). Erythrocyte sedimentation rate (91 mm/h) and C reactive protein (35 mg/l) suggested a pro-inflammatory status. High serum IgA was found (465 mg/dl). A renal biopsy identified glomerular sclerosis with IgA deposition, signs of diffuse vasculitis and tubular atrophia suggesting a diagnosis of IgA nephropathy. Chest X-Rays showed emphysema and diffuse nodularity suggesting diagnosis of silicosis. Chest tomography was also positive for mild signs of silicosis with silicotic nodules and without honeycombing. IgA nephropathy is the most common type of glomerulonephritis worldwide. Several clues suggest a genetic or acquired abnormality of immune system as a trigger of the increased production of IgA. In our case report, simultaneous kidney and pulmonary disease could suggest same triggers (e.g. exposure to virus, bacteria or environmental agents) inducing IgA synthesis and pulmonary immune system activation.

**Key words:** Dust, Work environments, Industrial hygiene, Occupational epidemiology, Small-medium enterprises

## Introduction

Despite the first report of kidney disease in silica-exposed workers dates more than 50 yr ago<sup>1</sup>, scientific evidences of “*silica nephrotoxicity*” remained limited, controversial, associated to anecdotal reports and few clinical and pathological studies<sup>2, 3</sup>. Although evidences still remain too sparse to be conclusive, silica is actually a

suspected risk agent for kidney diseases<sup>3</sup>.

First studies reported a clear tubular involvement; however subsequent availability of reliable biomarkers for early glomerular dysfunction (e.g. low molecular weight proteins and enzymes) suggested the silica dusts as a more complex nephrotoxic agent<sup>2</sup>. Indeed, in the last 10 yr, several major studies have linked prolonged exposure to crystalline silica with renal diseases and particularly glomerulonephritis<sup>3</sup>.

Pathologic properties of silica remain discussed. Actually, it could damage the kidney from: (a) direct toxicity of the particles reaching the tissue; (b) deposition in the

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kidney of immune-complexes following inflammation; (c) auto-immune mechanisms<sup>4</sup>), eventually activated by the strong immune reaction in the lung tissue<sup>3, 5</sup>).

Immune system over-activation, with subsequent auto-immune mechanisms induction, is also a cornerstone in silicosis progression in several pathogenetic models, and should justify frequent association of immune disease (e.g. Erasmus syndrome, rheumatic diseases) in silicotic patients<sup>6, 7</sup>.

IgA nephropathy (also known as Berger's Disease) is the most common immune-mediated glomerular disease worldwide<sup>8</sup>): here we present a case where renal involvement and signs of silicosis were simultaneously identified with a similar follow-up.

## Case Report

A 68-yr-old male, smoker (18.8 pack-year smoking history), Caucasian, was admitted to our hospital in October 2005 for proteinuria (2,800 mg/24 h) and reduced renal function (serum creatinine 2 mg/dl, GFR 35 ml/min), serendipitously stated during routine exams performed by the patient.

Renter, he started working 20-yr-old as a miner in a quarry of granite and sandstone, a sedimentary rock composed of sand-size mineral and rock grains, containing high levels of quartz. His tasks comported initial processing of sandstone blocks, performed mainly in open spaces, and their refining with mechanical and/or manual chisel—completed in working rooms poorly aerated.

Despite high levels of silica dusts in the work environment, he reported no mandatory use of airways protection devices during the first 25 yr of activity.

In conformity of Italian Legislation for medical surveillance on workplaces, he had annual medical examinations, comprising physical evaluation and chest X-ray, without clinical or radiological signs of silicosis or pneumoconiosis. Lung function tests were unavailable. After the year of retirement (1997), the patient performed annual blood and urine tests, stating normal glomerular filtration rate, and no signs of chronic inflammatory disease.

Urinalysis on admission confirmed nephritic-range proteinuria, microematuria, RBC casts and granular casts. Determination of sedimentation rate (91 mm/h), C reactive protein (35 mg/l) showed a pro-inflammatory status. High serum IgA was found (465 mg/dl).

A diagnosis of IgA nephropathy was proposed, and a renal biopsy performed identifying mild glomerular sclerosis with IgA deposition, signs of diffuse vasculitis and tubular

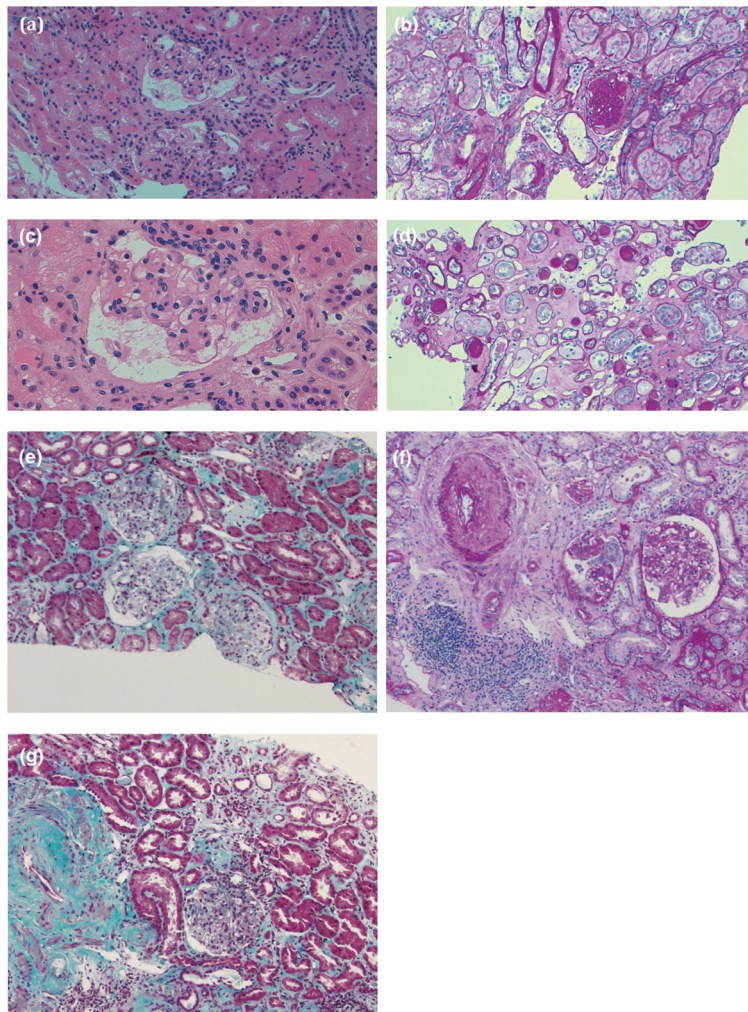
atrophy (Fig. 1).

Meanwhile, a routine chest X-Rays showed diffuse signs of emphysema, and stated diffuse, previously not reported nodularities, located in the upper right fields. A high resolution chest tomography (HRCT) was performed (Fig. 2) and resulted positive for diffuse centrilobular and paraseptal emphysema, more profuse in the upper lobes. Small size high density nodules appeared randomly diffused in all scans, whereas several pleural and subpleural high-density nodules were also identified, in particular in the dorsal upper left lobe. Scant peri-bronchial thickenings were also identified at right lower lobe. Mediastinal and hilar lymph nodes appeared enlarged, in particular at left hilum.

Because of occupational history of prolonged exposure to high levels of silica dust, and the radiological pattern, a mild form of chronic (active) silicosis was then supposed<sup>9</sup>): a confirmatory lung biopsy was not performed because of clinical conditions of the patients.

The simultaneous manifestations of kidney and lung disease were then supposed as consistent with a diagnostic hypothesis of IgA nephropathy associated with silicosis, and the patient started with specific immune-suppressing therapy. General conditions remained stable during the following 18 months, without clinical signs of progression of both renal and pulmonary disease.

Eventually, 18 months after the first episode, clinically relevant proteinuria (2,200 mg/24 h) was identified at urinalysis, suggesting a relapse of the IgA nephropathy (Fig. 3). A follow-up HRCT was then performed: a more diffuse pattern of centrilobular and paraseptal emphysema in upper lobes was identified (visual score: 50% ca. of total lung volume). Panlobular emphysema with diffuse bronchiectasis was identified at lower lobes, with extensive tissutal involvement. In general, a reticulo-nodular pattern of interstitial lung disease was evident (visual score 10%). In hilar regions, the nodules appeared also more diffuse (diameter 1–2 mm). Mediastinal and hilar lymph nodes were also of increased volume, without signs of calcification. Eventually, a panlobular emphysema with extensive tissutal involvement was identified in a setting of fibrotic non-specific interstitial pneumonia: signs of chronic active silicosis were also identified, confirming the previous diagnosis. A new cycle of immune-suppressing therapy was then started, achieving the temporary stabilization of both renal and pulmonary diseases.



**Fig. 1. Renal biopsy.**

Renal biopsies showed glomeruli with segmental thickening and enlargement of the mesangial axes (a), while a few ones were completely sclerotic (b), resembling a focal segmental glomerulosclerosis. Some of the glomeruli showed initial formation of florid crescents and small flocculo-capsular synechiae (e). Glomeruli had slightly thickened basal membranes and coarse mesangial deposits (c, f). Broad areas of tubular atrophy and interstitial fibrosis were present (d). Arteries has variable degree of fibrosis (g).

## Discussion

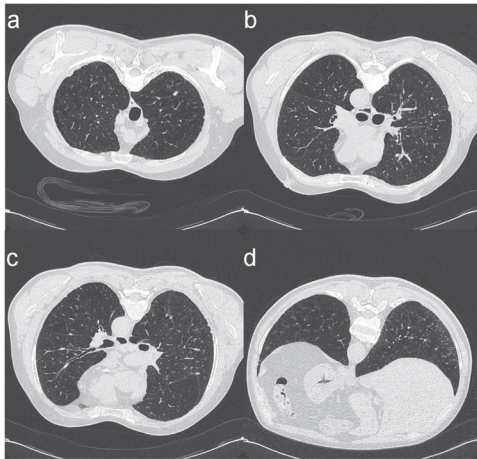
Silicosis is suspected to be an immune disease, involving activation of primitive highly conserved genes, like those involved in the Toll-Like Receptor (TLR) pathway<sup>6</sup>. Following these hypothesis, progression from silica dust deposition in lung parenchyma to diffuse fibrosis, silicotic nodule formation and, finally, honeycombing, would be accelerated in presence of favourable genetic pattern, explaining the presence of rapidly progressive pattern also for low environmental or occupational silica dust exposure<sup>6, 7</sup>.

IgA nephropathy, the most common type of glomerulonephritis worldwide, is also suspected as an immune disease<sup>8</sup>. Genetic or acquired abnormalities of immune system would be a trigger for increased production of IgA, which deposition in glomerulus induces and propagates renal disorder.

The simultaneous kidney and pulmonary involvement stated in this case report at diagnosis and follow up could suggest the same pathogenetic cascade, following exposure silica dusts and induced by virus, bacteria or environmental agents, able to induce massive IgA synthesis and pulmonary immune system activation.

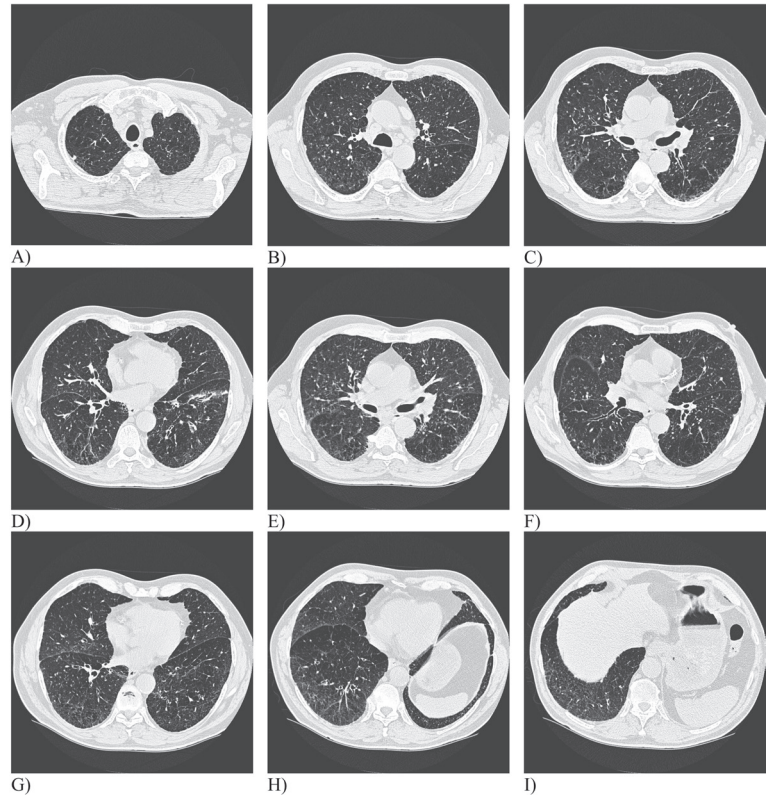
Despite the worldwide diffusion of IgA nephropathy and





**Fig. 2. HRCT performed after diagnosis of IgA nephropathy.**

The scans show diffuse centrilobular and para-septal emphysema, more profuse at higher lobes. High density nodules were randomly diffused: in subpleural position, they were accompanied by subpleural thickening, in particular at left superior lobe in dorsal position (a, b, c). Mediastinal lymph-nodes appeared enlarged, in particular at left hilum. Scant peribronchial thickenings were diffusely identified, and more evident in right lower lobe, whereas a mild, diffuse interstitial involvement was evident at left basis (images c and d). Prone position was necessary in order to avoid the gravity dependent opacities that could have obscured the subtle interstitial changes of this early stage of silicosis.



**Fig. 3. High resolution Chest Tomography performed at the relapse of IgA nephropathy (18 months after the first episode).**

The direct comparison with the previous scans suggests a significant progression of the underlying emphysema, with bilateral centrilobular and parasettall pattern and traction bronchiectasis at lower fields (D–I). High density nodularities appeared of increased diameter (1–2 mm) and more profuse, in particular at hilar and subpleural level (B–F, see for comparison Fig. 2, a–c). Interstitial involvement was also more evident, with a diffuse reticulo-nodular pattern (visual score 10%) (E–I). Mediastinal lymph nodes appeared enlarged, in particular at paratracheal (maximal diameter 2 cm) and para-aortic (maximal diameter 2.2 cm), deprived of calcifications, suggesting a recent, acute and massive activation of immune system (A–C).

several reports stating renal function alteration and high prevalence of IgA nephropathy in subjects exposed to silica dusts, we found only two other similar reports, but only one published in English-written medical journal<sup>10–13</sup>. Moreover, the recent retrospective study of Vacek *et al.* on 7,052 workers employed between 1947 and 1998 in the Vermont granite industry failed to assess a statistically significant association between silica exposure and death for nephritis and/or nephrosis (standardized mortality ratio 0.99, 95%CI 0.68–1.38)<sup>12</sup>. This fact could suggest only a serendipitous association between two unrelated pathologies, focusing on smoking history as the main individual risk factor for IgA nephropathy<sup>14</sup>.

However, several elements from this case report may suggest a different interpretation. On the one hand, the

cumulative smoking exposure of our patient was relatively low in order to explain *per se* both pulmonary and renal involvement<sup>13</sup>. On the other hand, previous reports suggest a parallel disease progression, where control of glomerulonephritis relapses would be associated with a better prognosis of lung disease<sup>10–13</sup>.

In our patient, an initially mild silica-induced lung disease, with few or no signs at conventional CXR, could have been worsened by the same immune system over-activation resulting in IgA nephropathy<sup>6–8</sup>, as the relapse identified at follow-up may suggest. In this case, a better control of renal disease progression and relapses would be the cornerstone to avoid or to slow the evolution of lung fibrosis towards severe honeycombing<sup>10, 11</sup>.

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