

Hypercalcaemia

A portent of sarcoidosis in cystic fibrosis

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فرط كالسيوم الدم نذير للساركويد في التليف الكيسي

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ABSTRACT: The coexistence of cystic fibrosis (CF) and sarcoidosis is rare. We report a 22-year-old male cystic fibrosis patient who presented multiple times to the Sultan Qaboos University Hospital, Muscat, Oman, in 2013. He was diagnosed with non-parathyroid-related hypercalcaemia and anterior uveitis, while computed tomography revealed mediastinal and abdominal lymphadenopathy and mild hepatosplenomegaly. These findings, in addition to the presence of calciuria and a high angiotensin-converting enzyme (ACE) level, confirmed a clinical diagnosis of sarcoidosis. The patient responded well to treatment with oral prednisolone which, over the course of two years, resulted in the near-complete resolution of parenchymal nodular infiltrates, regression of hilar lymphadenopathy, resolution of hypercalcaemia and the normalisation of his ACE levels. Diagnosing pulmonary sarcoidosis in CF can be challenging as most adult patients already have extensive lung disease. Physicians should be aware that hypercalcaemia may be an early manifestation of sarcoidosis in such cases.

Keywords: Sarcoidosis; Cystic Fibrosis; Hypercalcemia; Case Report; Oman.

المخلص: التواجد المشترك لمرض التليف الكيسي والساركويد أمر نادر. نعرض هنا حالة مريض يبلغ من العمر 22 عاما يعاني من مرض التليف الكيسي وتمت معانيته بشكل متكرر في مستشفى جامعة السلطان قابوس، مسقط، عمان، في عام 2013. وقد تم تشخيصه بفرط كالسيوم الدم الغير ناتج عن الغدة المجاورة للدرقية والتهاب العنقية الأمامي. كما أن الأشعة المقطعية أظهرت تضخم في العقد اللمفاوية في منطقتي المنصف والبطن وتضخم طفيف للكبد والطحال. هذه المعطيات مع وجود البيلة الكلسية وإرتفاع في الإنزيم المحول للأنجيوتنسين أكدت التشخيص السريري للساركويد. استجاب المريض بشكل جيد لعلاج البريدنيزولون عن طريق الفم على مدى سنتين مما نتج عنه اختفاء شبه كامل للعقد المتنية الرؤية و تراجع في حجم العقد اللمفاوية النقيرية، براء فرط كالسيوم الدم و إعتدال مستوى الإنزيم المحول للأنجيوتنسين إلى النطاق الطبيعي. تشخيص الساركويد الرئوي عند مرضى التليف الكيسي يشكل تحدي كون معظم مرضى التليف الكيسي البالغين يعانون من مرحلة متقدمة من أمراض الرئة. يجدر بالأطباء الإنتباه إلى أن فرط كالسيوم الدم قد يكون مظهر مبكر للساركويد في مثل هذه الحالات.

الكلمات المفتاحية: الساركويد؛ التليف الكيسي؛ فرط كالسيوم الدم؛ تقرير حالة؛ عمان.

SARCOIDOSIS IS A SYSTEMIC DISEASE CHARACTERISED by the formation of immune granulomas in various organs—mainly the lungs and lymphatic system—usually resulting from an exaggerated reaction to unidentified antigens in susceptible individuals.¹ On the other hand, cystic fibrosis (CF) is an autosomal recessive multisystem disorder that affects several organs, including the lungs, pancreas, liver and intestine.² The former disease has a prevalence of approximately 4.7–64 per 100,000 individuals per year worldwide, while the latter occurs in approximately one in 3,000–4,000 live births among Caucasians and is even less common in other ethnicities.^{1,2} In Oman, sarcoidosis is not uncommon, with a similar clinical picture to that reported elsewhere; in contrast, the prevalence of CF is estimated to be one in 2,738 individuals.^{3,4} As both conditions are quite rare, the unrelated coexistence of these diseases in a single patient is extremely unlikely. This case report describes

the successful response to sarcoidosis treatment in a CF patient who presented with hypercalcaemia, uveitis and mediastinal lymphadenopathy.

Case Report

A 22-year-old deaf and mute male patient with a long history of bilateral bronchiectasis was admitted to the Sultan Qaboos University Hospital, Muscat, Oman, with septic shock in 2013. Upon admission, his serum calcium levels were noted to be slightly elevated (2.65 mmol/L); however, they normalised following the administration of fluids. A diagnosis of CF was confirmed based on a sweat chloride test of 86 mmol/L, faecal elastase level of <50 µg/L and genetic testing showing a homozygous p.Ser549Arg mutation. Upon discharge, the patient was advised to manage his condition with nutritional and enzyme supplements, proper dietary habits and chest

Table 1: Laboratory test results of a 22-year-old male patient with cystic fibrosis

Variable	Result	Normal range*
Hb in g/dL	12.7	11.5–15.5
Platelet count in $\times 10^9/L$	253	150–450
WBC count in $\times 10^9/L$	6.2	2.2–10
INR	1.14	0.88–1.10
Serum ALT in U/L	3.7	0–41
Serum albumin in g/L	42	35–52
Serum CRP in mg/L	5	0–5
Calcium in mmol/L	3.08	2.15–2.55
ALP in U/L	165	40–129
Creatinine in $\mu\text{mol/L}$	134	59–104
24-hour urinary calcium in mmol	25.47	2.5–8
PTH in pmol/L	<0.1	1.6–9.3
PTHrP in pmol/L	0.7	<1.3
Vitamin A in $\mu\text{mol/L}$	2.67	1.72–2.52
Serum 25-OH cholecalciferol in nmol/L	29	75–250
1,25-OH vitamin D in pmol/L	228	48–144
Serum ACE in ACEU	116	12–68

Hb = haemoglobin; WBC = white blood cell; INR = international normalised ratio; ALT = alanine transaminase; CRP = C-reactive protein; ALP = alkaline phosphatase; PTH = parathyroid hormone; PTHrP = PTH-related peptide; OH = hydroxy; ACE = angiotensin-converting enzyme. *Age-specific reference ranges.

physiotherapy. Three months later, he was admitted again with septic shock. At this time, he complained of blurred vision and redness of the eyes. An ultrasound scan of the abdomen showed mild hepatosplenomegaly. The patient was diagnosed with bilateral non-granulomatous anterior uveitis and topical treatment was initiated.

Two months later, during a routine follow-up visit, a blood work-up revealed elevated calcium (3.08 mmol/L), alkaline phosphatase (165 U/L) and creatinine (134 $\mu\text{mol/L}$) levels, while all other electrolytes were within normal

limits. Upon examination, the patient was asymptomatic and denied any nausea, vomiting, weakness, lethargy or palpitations. His urinary and bowel movements were normal and his blood pressure was 104/60 mmHg. He was mildly dehydrated with a pulse rate of 110 beats/minute. An abdominal examination revealed that the liver was palpable 2 cm below the right costal margin. Moreover, his 24-hour urinary calcium level was very high (25.47 mmol), while serum parathyroid hormone (PTH) levels were low (0.01 pmol/L) and PTH-related peptide levels were normal (0.7 pmol/L). The patient was also vitamin D-deficient, with a serum 25-hydroxy (OH) cholecalciferol level of 29 nmol/L, despite an elevated 1,25-OH vitamin D level. His serum angiotensin-converting enzyme (ACE) level was 116 ACEU. The results of other basic laboratory tests were normal [Table 1]. *Sputum* microscopy, cultures and a polymerase chain reaction analysis for *mycobacterium tuberculosis* were negative. Autoimmune screening was also negative for rheumatoid factor, antinuclear antibodies, cytoplasmic-antineutrophil cytoplasmic antibodies (ANCA) and perinuclear-ANCA.

Computed tomography (CT) of the chest showed mediastinal lymphadenopathy, with the largest lymph node in the prevascular region measuring 2.7×1.0 cm, and minimal bilateral bronchiectatic changes [Figure 1]. A few faint irregular nodular opacities in the distal lung were also seen. A CT scan of the abdomen showed multiple lymph nodes, with the largest located in the *porta hepatis* measuring 2.5×1.4 cm; in addition, complete replacement of the pancreatic tissue by fat was observed, along with hepatosplenomegaly. A mediastinoscopy and lymph node biopsy was scheduled; however, the patient and his family refused the surgery. A bone marrow biopsy showed normal trilineage representation without any abnormalities.

A clinical diagnosis of sarcoidosis was made based on the presence of mediastinal and abdominal lymphadenopathy, anterior uveitis, mild hepatosplenomegaly, non-parathyroid-related hypercalcaemia, calciuria and elevated 1,25-OH vitamin D and ACE levels. The patient was prescribed steroids in the form of oral prednisolone.

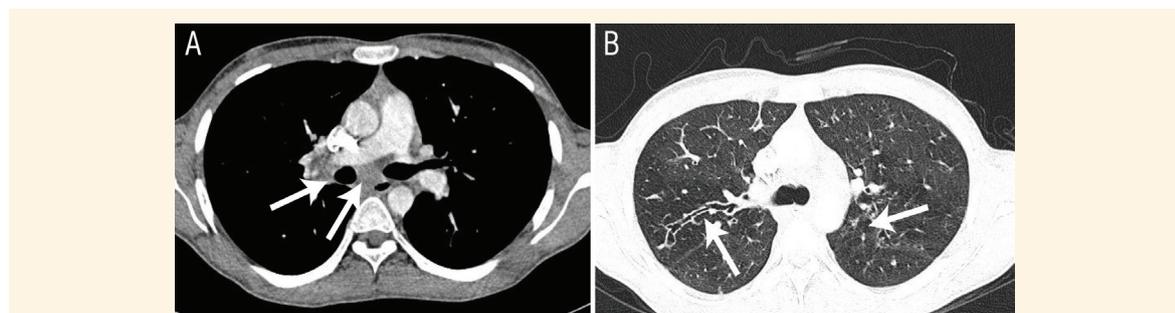


Figure 1: Computed tomography scans of the chest of a 22-year-old male cystic fibrosis patient with asymptomatic hypercalcaemia showing mediastinal lymphadenopathy and bilateral bronchiectatic changes (arrows).

His serum calcium levels normalised during the first few weeks of treatment and remained normal throughout the follow-up period; however, over the following month, he developed steroid-induced diabetes and required insulin. In addition, he was subsequently admitted twice, a year apart, primarily to optimise his CF treatment and for parenteral antibiotics.

Prednisolone treatment was continued for two years in tapering doses, resulting in the near-complete resolution of the patient's parenchymal nodular infiltrates, regression of hilar lymphadenopathy, resolution of hypercalcaemia and the normalisation of his ACE levels. The insulin was discontinued one month after the patient stopped taking prednisolone.

Discussion

Worldwide, there are very few reports documenting the coexistence of CF and sarcoidosis; this is possibly because the true incidence of sarcoidosis in CF is under-reported, as such patients already have widespread lung involvement.² The first published cases originated from the UK in 1987, in which Cooper *et al.* described two children with known CF, one of whom presented with multisystem disease.⁵ Since then, a few reports have been published detailing CF patients presenting with either pulmonary or systemic symptoms of sarcoidosis.^{6–11} However, to the best of the authors' knowledge, the current case is the first in which asymptomatic hypercalcaemia was an early sign of sarcoidosis in a CF patient.

In view of the low prevalence of both conditions, there may be a pathogenic link between CF and sarcoidosis. This may be due to either a common genetic predisposition or an acquired immune response defect. Both sarcoidosis and CF patients demonstrate defective T cell-mediated immune function and enhanced B cell activation.⁵ However, CF is caused by a mutation of the *cystic fibrosis transmembrane regulator (CFTR)* gene located on chromosome 7, while sarcoidosis susceptibility, phenotype and prognosis is associated with many gene variants, including variations in the *major histocompatibility complex class II* gene subgroup.^{1,2} Nevertheless, although previous research has suggested that there is a high frequency of *CFTR* mutations in patients with sarcoidosis, the findings of another moderately-sized study did not support an association between *CFTR* mutations and sarcoidosis phenotype.^{12,13}

The altered immune response in CF secondary to chronic infection could also be responsible for the development of sarcoidosis.⁵ Antigen presentation may be potentiated by tissue damage exposing the raw bronchial mucosal surfaces; as a result, sarcoid granulomas could develop in response to immune stimulation by these antigens originating from microorganisms or from glyco-

proteins and polypeptides generated by monocyte-macrophage hyperactivity.^{5–7} It is worth noting that *Mycobacterium*, *Propionibacterium* and various fungi, viruses and spirochetes have also been implicated in the development of sarcoidosis.¹ As such, further research is necessary to confirm a link between the two conditions and to establish a causative mechanism.

Apart from sarcoidosis, hypervitaminosis A may be another explanation for the hypercalcaemia noted in the current case. Chronic vitamin A toxicity can result from the ingestion of large amounts of vitamin A over a long period, with hypercalcaemia resulting from the direct effect of vitamin A on the bone, parathyroid glands or both.¹⁴ However, in the present case, the patient had slightly high serum calcium levels prior to his CF diagnosis and recommendations for vitamin A supplementation. At the time, his serum calcium levels would have normalised as a result of the fluids given to manage the shock. Accordingly, a clinical diagnosis of sarcoidosis was made based on the presence of mediastinal and abdominal lymphadenopathy, anterior uveitis, mild hepatosplenomegaly, non-parathyroid-related hypercalcaemia, calciuria and elevated 1,25-OH vitamin D and ACE levels.

Conclusion

A pathogenic link may exist between sarcoidosis and CF in terms of a common genetic predisposition or an altered immune response; however, this supposition as yet remains hypothetical and requires further research for confirmation. Regardless, a diagnosis of pulmonary sarcoidosis in CF is challenging as most adult patients already have extensive lung disease. In such cases, hypercalcaemia may be an early sign.

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