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Recrudescence of Sarcoidosis on stopping Hydroxychloroquine pre-contact prophylaxis for COVID-19

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Abstract

Presentation

We report the case of a 43-year-old Indian man, living in Ireland, who presented 5 years previously with severe fatigue and marked peripheral lymphadenopathy.

Diagnosis

Chest x-ray revealed stage 1 bi-hilar lymphadenopathy. He was diagnosed with sarcoidosis on right inguinal and mediastinal lymph node biopsies after careful exclusion of Tuberculosis.

Treatment

His disease spontaneously remitted and then in May 2020 he developed an acute exacerbation similar to his original presentation. A further inguinal lymph node biopsy again confirmed sarcoidosis.

Discussion

This exacerbation occurred two weeks after a 2-week course of hydroxychloroquine 200mg bd taken for pre-contact prophylaxis for COVID-19. There were no interceding infections or vaccinations. His symptoms settled over the ensuing weeks without treatment, and he remains well as of early 2024. To our knowledge, this is the first description of an exacerbation of previously quiescent sarcoidosis following discontinuation of short-course hydroxychloroquine.

Introduction

Sarcoidosis is a multi-system disease of unknown aetiology characterised classically by non-caseating granulomas on histology. Ethnicity has a marked effect on prevalence and phenotype of the disease. About 60% of patients spontaneously remit. Hydroxychloroquine (HCQ) remains a useful second line agent in the treatment of sarcoidosis[1]. We report a case of an exacerbation of sarcoidosis following a short course of HCQ, which to our knowledge, has never been described before.

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Case Report

We report a 41-year-old Indian man, living in Ireland, who was diagnosed with sarcoidosis 5 years previously. His main symptom was severe fatigue and on examination he had marked, generalised lymphadenopathy. Chest x-ray (Figure 1) was Scadding stage 1 with symmetrical hilar lymph node enlargement. HRCT Thorax revealed mediastinal and hilar lymphadenopathy with no interstitial lung disease (Figure 2). The main differential diagnosis was Tuberculosis and lymphoma. Lymph node excision biopsy confirmed non–caseating granulomas, as did mediastinal biopsy by EBUS, with negative stains for acid-fast bacilli, negative PCR for *Mycobacterium tuberculosis* and lymph node culture.

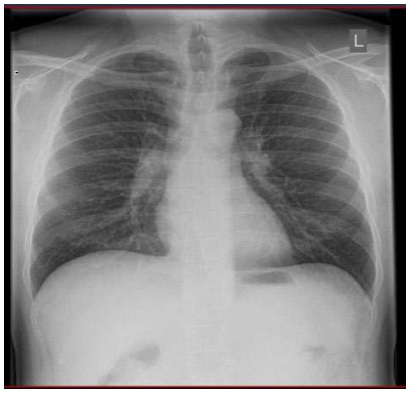

Figure 1 Chest x-ray at presentation shows Scadding Class 1 with bilateral hilar enlargement and clear lung fields.

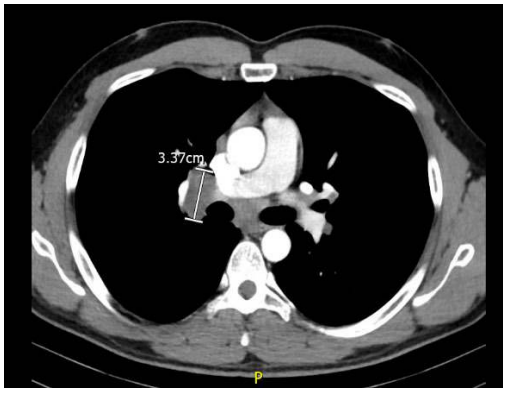

Figure 2 CT scan showing marked right hilar and sub-carinal lymphadenopathy

As the organ involvement was minimal he was not started on treatment. Over time his energy improved and chest x-ray normalised. In May 2020 he commenced hydroxychloroquine (HCQ), at a dose of 200 mg BD for 2 weeks, as pre-contact prophylaxis for COVID-19. Two weeks after stopping HCQ , he had an exacerbation of his sarcoidosis. His peripheral lymph nodes, particularly the inguinal nodes, became very enlarged and tender, he had a dry cough and he was very listless.

His chest x-ray revealed Scadding stage 2 sarcoidosis (Figure 3) and HRCT confirmed bi-apical mild interstitial lung disease (Figure 4). He had normal spirometry with an FEV1 of 106% predicted, FVC of 104% predicted and gas transfer of 72% predicted which was 10% lower compared to his gas transfer at initial presentation. He had a further, inguinal lymph node excision biopsy, which again showed sarcoidosis with negative acid-fast bacilli stain, negative PCR and negative gland culture for *Mycobacterium tuberculosis.* His throat swab was negative for COVID-19 infection and he had had no recent COVID-19 vaccinations. He improved significantly over the ensuing weeks and we,

therefore, withheld treatment. Most recent chest x-ray is normal as is his lung function tests as of late 2023.

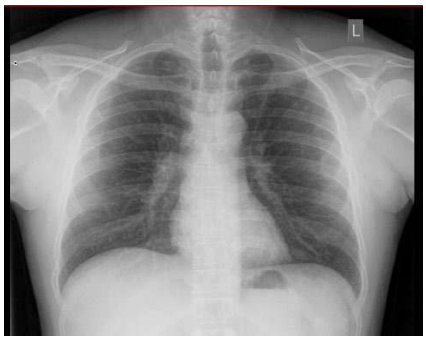

Figure 3 Chest x-ray at re-presentation shows Scadding class 2 with some resolution of the hilar lymphadenopathy but new nodularity in the upper zones.

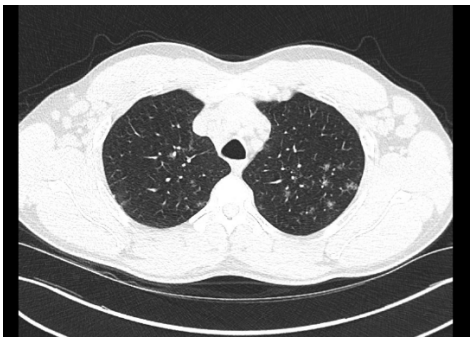

Figure 4 CT scan at re-presentation shows mild poorly marginated nodularity in both upper lobes

Discussion

We cannot be certain what caused this acute exacerbation of sarcoidosis. He had not had a HRCT of thorax since diagnosis, so it is possible there was sub-clinical progression in the interim. To our knowledge, an acute exacerbation of previously quiescent sarcoidosis following a short course of HCQ has never been described before. It is plausible that withdrawal of HCQ caused this as his disease had been stable off treatment 2 years prior to, and 3 years post, this event. Moreover, if you do not require treatment in the first 2 years after diagnosis that would normally portend an excellent prognosis in sarcoidosis.

The prevalence of sarcoidosis in India is high with an estimated prevalence of between 61-150 per 100 000 patients[2]. Indian patients tend to present at an older age than their western counterparts with males presenting in their 5th decade and females in their 6th decade of life[3]. 17% of Indian patients get peripheral lymphadenopathy which is also similar to Europeans. Interestingly, nearly 30% of sarcoidosis patients in India have had a trial of anti-tuberculosis treatment pre-diagnosis[4].

HCQ is used in a variety of auto-immune diseases such as SLE (5), Rheumatoid Arthritis[6] and Anti-Phospholipid Syndrome[7]. The evidence for its benefit in SLE is clear and it is recommended as first-line therapy[5]. In common with RA, it appears to delay disease progression and has a favourable effect on serum lipids and cardiovascular risk.

HCQ has also been used extensively as a second line agent for sarcoidosis since at least the mid 1980's. It is usually very well tolerated and has been shown to be efficacious in cutaneous sarcoidosis[8], sarcoidosis-related arthritis[9] and neurosarcoidosis[10]. Due to gastrointestinal side-effects and potential ocular toxicity HCQ is often stopped abruptly, however, despite this there are

no published reports describing a similar phenomenon[11]. There is a solitary case report from 1996 describing a patient with non-caseating granuloma on liver biopsy on malaria prophylaxis with a pyrimethamine / chloroquine combination with no other organ involvement[12]. This would represent a localized drug reaction not sarcoidosis.

In a publication in 2020[12] interrogating Vigibase, which is a WHO database for reporting on side-effects of medicinal compounds, there were 8 reports of HCQ causing a sarcoidosis-like reaction (SLR). Unfortunately, these reports were never published in case report form. In SLRs the patient is usually still on the drug at diagnosis and the condition often improves rapidly after discontinuing the drug. From the same study the commonest drugs causing SLR in decreasing frequency were TNF-α inhibitors (infliximab, etanercept, adalimumab and golimumab), interferons and immune checkpoint inhibitors (pembrolizumab, ipilimumab and nivolumab). Other selected drugs which were less frequently associated with SLR were rituximab, omalizumab, BRAF or MEK inhibitors and pulmonary hypertension drugs. Our patient took HCQ as pre-contact prophylaxis for protection from COVID-19 as, at that time, it was thought to have good anti-SARS-CoV-2 activity. However, there is now no known proven efficacy for this approach[13].

The mechanism of HCQ action is not fully elucidated and most of what we know is extrapolated from studies into its effect in SLE. It appears to have several different effects. It is lipophilic and, therefore, can traverse cell membranes. It is also an alkaline agent and on entering immune effector cells it stabilizes the lysosome by raising the pH, thus interfering with cell signalling[6]. Binding of HCQ to nucleic acids may mask their Toll-like receptor (TLR)-binding epitope leading to a reduction in interferon -ϒ production[14]. Moreover, HCQ may partially inhibit interferon-ϒ release from activated plasmacytoid dendritic cells by blocking the response to TLR9[15]. Interferon -ϒ has been shown to be a key driver in granuloma formation[16].

In addition, HCQ subverts antigen presentation to MHC class II molecules which is a critical step in the pathogenesis of sarcoidosis (17). The drug can also ameliorate pro-inflammatory cytokine production such as IL1β, IL6 and IL17 and TNFα by macrophages[18]. In a recent study in SLE, serum levels of TNF-α, IL-6, IL-8, VEGF-A, IL-1ra, and IL-2 were all significantly lower after 3 months treatment with HCQ (19). TNF-α is thought to be a chemoattractant for neutrophils and monocytes which play a key role in granuloma formation[1,20].

There was no evidence of interceding infection or vaccination which may have acted as an antigenic stimulus to an exacerbation of sarcoidosis. HCQ has not been associated with an increased risk of opportunistic infection or COVID-19[21]. It was previously thought that HCQ had a very long half-life possibly up to 40-50 days due to extensive tissue binding (22). However more recent work suggests a much shorter half-life of 5 days[23] making the timeline of HCQ withdrawal more plausible as a possible cause of the exacerbation. Withdrawal of the drug may have led to a rebound phenomenon of some, or all the mechanisms mentioned previously.

In conclusion, we present a case of an acute exacerbation of sarcoidosis previously quiescent for 2 years on no treatment. It is possible that the abrupt start and stop of this medication provoked this immunological response and in future, we may have to consider a slower phase out of this treatment.

Declarations of Conflicts of Interest:

None declared.

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