

Sarcoidosis Following Treatment with Medical Cannabis

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PATIENT DESCRIPTION

Our patient was a 48-year-old man who had been diagnosed with fibromyalgia 4 years prior to presenting with sarcoidosis, according to the criteria of American College of Rheumatology (ACR). Symptoms included diffuse musculoskeletal pain, fatigue, sleep problems, tenderness at all classic tender points without synovial swelling, and normal serology. The patient was initially treated with different medications including dipyrrone, duloxetine, and tramadol, which was associated with urinary retention.

In December 2017, the patient started smoking 20 grams of medical cannabis (MC) each month. The MC was provided by Tikun Olam, a local cannabis growing company using two species, Alaska (predominantly sativa with 18% of tetrahydrocannabinol-9-delta-) THC and 1% cannabidiol (CBD) during the day and Erez in evening (predominantly Indica, 18% of THC and 1% of CBD). Two months later he switched to evaporation due to throat irritation from smoking.

Ten months after starting MC, the patient reported a dry cough and was approved for another 10 grams of MC by oil. Sixteen months following the treatment of cannabis patient had a computed tomography (CT) scan of the chest showing enlarged mediastinal lymph nodes. One

month later patient had bronchoscopy and a transbronchial biopsy that showed non-caseating granuloma, suggestive of sarcoidosis. Angiotensin-converting enzyme level was within normal limits. A request for MC oil usage only was submitted to the Israeli medical cannabis agency. The patient started taking systemic steroids that was switched later to inhaled steroids with improvement of the cough.

COMMENT

Sarcoidosis was reported previously in one case only, that of an 18-year-old male who was described as a regular tobacco and occasional cannabis smoker [1]. In that case, sarcoidosis developed one year after starting cannabis. The question remains whether cannabis had an etiopathogenic role in the development of sarcoidosis.

Although cannabis is the most widely used illicit drug in the world, there is relatively limited published data regarding its effects on the respiratory system. Studies have suggested that cannabis has different effects on the respiratory system than tobacco smoking. These effects include bronchitis, large airway inflammation, symptoms of bronchitis, increased airway resistance, and lung hyperinflation [2]. There is no convincing evidence that smoking cannabis leads to chronic obstructive pulmonary disease and airflow obstruction. However, cases of bullous emphysema among cannabis smokers has been reported. There is inconclusive evidence regarding the association with respiratory malignancies.

Cannabis smoke contains various can-

nabinoids, for example cannabidiol which also have anti-inflammatory and antifibrotic properties, with the unconfirmed hypothesis that these properties can partially modulate the deleterious action of cannabis smoke.

However, airway mucosal inflammation, sputum production, and wheezing with a chronic cough similar to those evoked by tobacco smoking, were reported following cannabis consumption. These effects were not mediated by CB1 receptors [3]. Similar effects also exist regarding vascular and goblet cell hyperplasia, cellular disorganization, and metaplasia.

The effects of cannabis on lung function remain unclear and may be different from those of tobacco. Cumulative cannabis use was associated with higher forced vital capacity, total lung capacity, functional residual capacity, and residual volume [2].

Regarding risk factors in general for the development of sarcoidosis, a population-based nested controlled study found that tobacco smoking has a lower risk for the development of sarcoidosis, while obese people have a higher risk. Other risk factors include, familial clustering of autoimmune disease and previous tonsillectomy or appendectomy.

At the cytokine level, any T-cell-associated cytokines have been implicated in the immunopathogenesis of sarcoidosis, but it is becoming apparent that IL-12 cytokine family members including IL-12, IL-23, IL-27, and IL-35 are also involved. Although the members of this unique cytokine family are heterodimers of similar subunits, their biological functions are very

diverse. While IL-23 and IL-12 are pro-inflammatory regulators of Th1 and Th17 responses, IL-27 is bidirectional for inflammation and the most recent family member IL-35 is inhibitory. It is interesting to note that sarcoidosis had developed in two cases treated with anti-IL-1 [4,5]. It is known that cannabis has an anti-IL1 effect, so down-regulating IL-1 could have an important role in the development of sarcoidosis. Further studies are needed on this issue.

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Capsule

Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

PD-1 plus CTLA-4 blockade is highly effective in advanced-stage, mismatch repair (MMR)-deficient (dMMR) colorectal cancers, yet not in MMR-proficient (pMMR) tumors. **Chlabi** et al. postulated a higher efficacy of neoadjuvant immunotherapy in early-stage colon cancers. In the exploratory NICHE study, patients with dMMR or pMMR tumors received a single dose of ipilimumab and two doses of nivolumab before surgery, the pMMR group with or without celecoxib. The primary objective was safety and feasibility; 40 patients with 21 dMMR and 20 pMMR tumors were treated. Three patients received nivolumab monotherapy in the safety run-in. Treatment was well tolerated and all patients underwent radical resections without delays, meeting the primary endpoint. Of the patients who received ipilimumab + nivolumab (20 dMMR and 15 pMMR tumors), 35 were evaluable for efficacy

and translational endpoints. Pathological response was observed in 20/20 (100%; 95% exact confidence interval (CI): 86–100%) dMMR tumors, with 19 major pathological responses (MPRs, ≤ 10% residual viable tumor) and 12 pathological complete responses. In pMMR tumors, 4/15 (27%; 95% exact confidence interval 8–55) showed pathological responses, with 3 MPRs and 1 partial response. CD8+PD-1+ T cell infiltration was predictive of response in pMMR tumors. These data indicate that neoadjuvant immunotherapy may have the potential to become the standard of care for a defined group of colon cancer patients when validated in larger studies with at least 3 years of disease-free survival data.

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Capsule

How Salmonella gets a gut feeling

Salmonella enterica commonly causes gastroenteritis, but it can also disseminate from the gut to cause invasive infections. **Carabajal** and colleagues found that *Salmonella* modified its virulence gene expression program in response to long-chain unsaturated fatty acids such as those found in the gut and in bile. Oral

administration of conjugated linoleic acid enhanced both gut colonization and dissemination of *Salmonella* to the spleen. Long-chain unsaturated fatty acids thus fine-tune the fate of *Salmonella* during infection.

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"Your talent is God's gift to you. What you do with it is your gift back to God"

Leo Buscaglia (1924–1998), American author and motivational speaker, and a professor at the University of Southern California