Interferon-Induced Hypercalcemia

by Iliana Doycheva, Anthony Michaels, Cynthia Levy

We present a case of interferon-induced hypercalcemia in a 57-year-old male being treated for hepatitis C infection. The patient had been on peg-interferon and ribavirin for five months before his first hospitalization for elevated calcium level and prerenal azotemia. Extensive work-up at baseline was unrevealing. He was managed symptomatically and discharged home. However, in the next four months he required three additional hospitalizations due to refractory hypercalcemia despite discontinuation of interferon, and steroid treatment was initiated. Sarcoidosis is a rare but well-recognized complication of interferon-based therapy. The uniqueness of this case relies on its presentation with isolated symptomatic hypercalcemia and negative work-up at baseline, as a repeat angiotensin-converting enzyme (ACE) level only became elevated later in the patient’s course. We offer a review of the literature and a discussion on proposed pathogenesis and clinical course of interferon-induced sarcoidosis.

A CASE PRESENTATION

A 57-year-old Caucasian male with past medical history of hepatitis C, hypertension and depression, was admitted to our hospital with nausea, vomiting, decreased appetite and 20 pound weight loss over the last month. He was a former smoker and drinker, used cocaine intranasally in the past, but denied intravenous drugs. On routine check-up, six months prior to the current hospitalization, he was diagnosed with Hepatitis C. His initial HCV-RNA was 4,000,000 UI/ml, and he was genotype 2b. A liver biopsy revealed modified Knodell Histologic Activity Index (HAI) grade 6 and Ishak stage 3 out of 6 for fibrosis. Treatment was started with peginterferon alfa-2a 180mcg weekly and ribavirin 800 mg daily. During therapy he had developed nausea, dyspepsia, joint pains, lower extremity edema, rash, and insomnia, all of which were appropriately treated.

On admission he showed signs of volume depletion, with elevated BUN 36 mg/dL, creatinine 2.4 mg/dL and a serum calcium level of 14.1 mg/dL (ionized calcium 8.6 mg/dL). Intravenous hydration was initiated, followed by administration of diuretics. The patient underwent extensive work-up for hypercalcemia including a PTH-intact (low normal), PTH-related protein (normal), thyroid function tests (normal), serum and urine protein electrophoresis (normal), HIV test (negative), ACE level (normal), total vitamin D and 25- OH vitamin D levels (low), vitamin A level (normal), a bone scan (normal), and the computed tomography (CT) scan of his chest, abdomen, and pelvis was only significant for hepatomegaly. During that admission, both hypercalcemia and renal function normalized; he was discharged home to continue with antiviral therapy.

He presented for a new admission two months later with nausea, vomiting and poor oral intake. His laboratory tests revealed a serum creatinine of 1.6 mg/dL with a calcium level of 14.1 mg/dL. He received intravenous hydration with a moderate effect on the calcium level. Calcitonin and one dose of pamidronate were given as part of the treatment. His clinical (continued on page 53)
symptoms, renal function and calcium level again improved to normal and he was discharged. This time, interferon and ribavirin were discontinued.

In the next two months the patient had two admissions for fatigue, decreased appetite, and nausea due to hypercalcemia. An ACE level was repeated and was high at 168 U/L from an initial normal level, his 1.25 dihydroxy vitamin D level was elevated, and a 24h urine collection revealed hypercalciuria. In order to rule out primary hyperparathyroidism as the PTH levels were not accordingly suppressed (table 1), a technetium 99m sestamibi test was performed and was subsequently negative. There were no pulmonary infiltrates or lymphadenopathy found, but because of the persistent symptomatic hypercalcemia and concern for sarcoidosis, he was started on low dose oral steroids. On follow-up three weeks later, the patient’s symptoms markedly improved and his calcium level normalized.

**DISCUSSION:**

Hepatitis C (HCV) infection is a global problem with an estimated prevalence of 1.6% in the United States (US) [1, 2]. Current standard therapy for HCV includes pegylated interferon in combination with ribavirin. Adverse effects of Hepatitis C treatment are common, as exhibited by our patient, including interferon-induced sarcoidosis (IIS) [3]. Even though this patient did not have pulmonary or other obvious organ involvement, sarcoidosis remained as a potential etiology for the hypercalcemia, given the elevated ACE level, low-normal PTH and elevated 1,25 dihydroxy vitamin D level, as well as the fact that other etiologies were appropriately ruled out. Specifically, primary hyperparathyroidism, hyperthyroidism, milk-alkali syndrome, vitamin D intoxication, malignancy, and drug-induced hypercalcemia were all excluded. Tertiary hyperparathyroidism was not supported by his laboratory tests, and after his third admission it became clear that the hypercalcemia was occurring irrespective of the renal function.

IIS was first described in 1987 by Abdi et al. in a patient treated with interferon beta [4]. Several years later reports associating interferon-alfa (IFN-α) therapy for treatment of HCV and newly developed sarcoidosis started arising and since then, several case reports have been published. The mean time to onset of symptoms was 11 months (range 1-60 months) after initiation of treatment [5, 6]. Usually the clinical presentation of IIS is insidious and can be confused with constitutional side effects of interferon therapy. The most commonly

Table 1: Key Laboratory Data

<table>
<thead>
<tr>
<th></th>
<th>Calcium (mg/DL) (8.4-10.5)</th>
<th>Phosphate (mg/dL) (2.5-4.6)</th>
<th>Creatinine (mg/dL) (0.6-1.2)</th>
<th>PTH Intact (pg/ML) (10-65)</th>
<th>ACE Level (U/L) (9-67)</th>
<th>Vit D Total (ww) (20-100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st admission</td>
<td>14.1 → 10.8</td>
<td>3.0</td>
<td>2.4</td>
<td>20.6</td>
<td>51</td>
<td>19</td>
</tr>
<tr>
<td>2nd admission</td>
<td>13.3 → 10.8</td>
<td>3.6</td>
<td>1.6</td>
<td>11.6</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>3rd admission</td>
<td>12.2 → 10.8</td>
<td>3.3</td>
<td>1.4</td>
<td>13</td>
<td>168</td>
<td>6</td>
</tr>
<tr>
<td>4th admission</td>
<td>13.6 → 12.1</td>
<td>2.6</td>
<td>1.3</td>
<td>24.1</td>
<td>168</td>
<td>-</td>
</tr>
<tr>
<td>After 1 month of oral steroids</td>
<td>9.4 → 10.1</td>
<td>3.0</td>
<td>0.8</td>
<td>46.6</td>
<td>51</td>
<td>21</td>
</tr>
</tbody>
</table>
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affected organs are lungs and skin. However, many other manifestations have been described, including central and peripheral nervous system, parotid glands, eyes, heart, lymph nodes, or liver involvement, as well as Lofgren’s syndrome. Symptomatic hypercalcemia occurs in approximately 10% of patients, while hypercalcemia is even more frequent and can be found in up to 40% of the patients [7, 8]. Almost always hypercalcemia presents in conjunction with other symptoms which makes our case unique in presentation [8, 9, 10].

The precise pathophysiologic mechanism of IIS is not completely understood. In naturally occurring sarcoidosis, granulomatous inflammation is characterized by expression of T helper-1 (Th-1) cytokines, interleukin-2 (IL-2) and interferon gamma (IFN-γ) with suppression of T helper-2 (Th-2) cytokines, interleukin-4 and interleukin-5. Interleukin-12 (IL-12) which plays an important role in Th-1 response was also found to be upregulated [11]. Similarly, it is believed that in IIS interferon stimulates antigen-presenting cells (APC) by promoting overexpression of major histocompatibility complex class II antigens and stimulating monocytes to release IL-12. In turn, IL-12 activates Th-1. It is also known that interferon stimulates nature killer cells to produce IFN-γ and directly activates CD4+ T helper-0 toward Th-1 immune response. This way activated Th-1 cells maintain the activation of APCs and Th-1 cells through IL-2 and IFN-γ, thus leading to granulomas formation [6]. In addition, expansion of a CD4+ CD 28 negative cell subset was demonstrated in one patient with ISS. This T-cell subset has been associated with high proinflammatory and tissue damaging properties [12]. From the other side, hypercalcemia in sarcoidosis is secondary to an overproduction of 1,25 dihydroxy vitamin D by activated 1α-hydroxylase, produced by macrophages within the granulomas and pulmonary alveoli [7, 8]. IFN-γ stimulates 1α-hydroxylase activity in macrophages and IFN-α can lead to an environment with higher levels of IFN-γ [7].

The possible synergistic effect of Ribavirin to interferon in inducing sarcoidosis is unclear. More patients reported to have IIS over the past years received combination therapy and thus it is difficult to assess the effect of Ribavirin alone. Ribavirin might be contributing to the pathogenesis of IIS by selectively inhibiting Th-2 mediated cytokine production while preserving Th-1 cytokine production [13].

Interestingly, several investigators reported development of sarcoidosis in untreated patients with chronic HCV infection. The hypothesized mechanism is that the persistent viral infection might trigger cellular immune response leading to clinical sarcoidosis [14].

Usually IIS has a benign course and resolves without treatment. In patients with progressive or serious symptoms steroids have shown beneficial effect. However, they can increase replication and recurrence of HCV. Other therapies that have been used include hydroxychloroquine, minocycline, cytotoxic agents (methotrexate, azathioprine, chlorambucil, cyclophosphamide), cytokine modulators (thalidomide and pentoxifylline) and anti-tumor necrosis factor agents (etanercept and infliximab) [15]. Infliximab in particular, has been used and reported being successful in a patient presenting with hypercalcemia [8]. In our patient, discontinuation of interferon and ribavirin did not lead to normalization of calcium but he significantly improved with low dose steroids.

Further studies clarifying the independent role of interferon, Ribavirin and hepatitis C infection itself are needed to better understand IIS in patients on treatment for hepatitis C. Interferon continues to be increasingly used in various therapeutic regimens, and care givers should continue to be aware of its immunomodulatory properties and side effects.

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