Editorial

"Yellow Nail Syndrome" and Rheumatoid Arthritis

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A nail dystrophy characterized by the slow growth of nails and their yellowish discoloration, the so-called yellow nail syndrome (YNS), has been associated with various conditions including rheumatoid arthritis (RA).

We reviewed the histories of RA patients reported in the literature and our own cases. Most of the RA patients with YNS had been treated with the anti-rheumatic agents D-penicillamine and bucillamine. In non-treated patients, spontaneous YNS was very rare. However, pulmonary diseases, edema and other systemic complications were frequently observed in both drug-induced and spontaneous YNS associated with RA. Although the nail changes and systemic complications are probably due to different causes in drug-induced YNS, a careful search for systemic complications are necessary in patients who develop nail changes.

The exact mechanism of nail growth retardation is not understood in patients with YNS, including those with drug-induced YNS. The nail changes in the latter were not associated with deficiencies of inorganic elements in either nails or sera.

(Key Words: yellow nail syndrome, rheumatoid arthritis, bucillamine, D-penicillamine)

INTRODUCTION

The term, yellow nail syndrome (YNS), was first used by Samman et al (1964) to describe a nail dystrophy characterized by discolored (yellow) nails associated with edematous conditions (6). The nail changes were originally considered to be caused by the slow growing of nails due to defective lymphatic drainage (4, 6). However, the nail changes were shown to be associated not only with chronic lymphoedema, but also with various pulmonary complications, cardiac diseases, chronic sinusitis, certain immune deficiency states, and, rarely, rheumatoid arthritis (RA) with or without D-penicillamine (D-Pen) treatment (1, 3, 5, 7, 8, 10). Bucillamine (BUC), recently developed in Japan as a slow-acting anti-rheumatic drug (SAARD), has also been reported to induce yellowish nail changes (2). The exact mechanism of nail growth retardation is still unclear in patients with YNS, including those with drug-related YNS.

In this paper we present case reports on two RA patients with BUC-induced YNS; review the clinical features of RA patients with YNS as reported in the literature; and discuss the cause(s) of drug-related YNS.

CASE PRESENTATIONS

Case 1. A 49-year-old female (RA, stage IV, class II). She has suffered from RA since December, 1974. Gold sodium thiomalate (GST) has been effective in managing her arthritis without adverse effects for 12 years. A second SAARD treatment with D-pen, 100–200 mg/day, was halted within one month because of microhematuria. She developed skin rashes 2 weeks and one month after her 3rd and 4th courses of SAARD treatment, with sulphasalazine (SAS) and auranofin (Au), respectively. She has been taking prednisolone, 2.5–5 mg/day since 1987, in addition to a non-steroidal anti-inflammatory drug (NSAID), diclofenac sodium, 75 mg/day. Treatment with BUC was started January 6, 1988 (Figure 1). The treatment was effective, although temporarily withheld because of an oral ulcer. She noticed that all the nails of her...
fingers and toes had become yellowish in August, 1989, when the total amount of BUC administered had reached 36 g (Figure 2). The daily dosage of BUC was decreased to 100 mg because of the possibility that it might have caused her nail changes. Her nails improved slightly, but she then developed a chronic non-productive cough in February, 1990. Abnormal findings were not detected by repeated chest X-ray studies. In November, 1990, the BUC treatment was stopped, although other adverse effects of BUC were not observed. She had no peripheral edema and her serum immunoglobulin G, A, and M levels were not

49-year-old female K.L. (RA, stage IV, class II)

Fig. 1. Clinical course of case 1: Abbreviations as follows: Au = auranofin; BUC = bucillamine, RAHA = titers of serum rheumatoid factors determined by hemagglutination test; ESR = erythrocyte sedimentation rate.

Fig. 2. Fingers of case 1 showing yellow discoloration of nails.
decreased. After termination of the BUC treatment, her nail changes and respiratory symptoms gradually disappeared.

**Case 2.** A 45-year-old male (RA, stage III, class II). He had a history of pulmonary tuberculosis when he was 18 years old, which was treated. He developed RA in 1981, and had received injections of GST for 19 months. However, the GST treatment was not effective. The second and third treatments with D-pen or SAS were stopped because he developed either proteinuria or fever 2 weeks after each course of treatment. Thereafter, he received lobenzarit disodium (CCA), 240 mg/day, for 12 months, but the agent was considered to be not-effective. BUC treatment, 300 mg/day, was started in November, 1987, and was effective (Figure 3). In December, 1989 when the total dosage of BUC had reached 140 g (Figure 4), he noticed that the nails of his fingers and toes had become yellowish. Since BUC was suspected as the cause, the daily dosage was decreased to 200 mg. However, the nails of his great toes spontaneously separated (onycholysis) in April 1988.

**Fig. 3.** Clinical course of case 2: CCA = lobenzarit disodium. Other abbreviations are as in Figure 1.

**Fig. 4.** Fingers of case 2 showing yellow discoloration and thickening of all nails.
and July, 1990 (Figure 5), and the dosage of BUC was further decreased to 100 mg/day. In July, 1990, he complained of an increasingly severe cough with sputum which had been developing since May, 1988. Chest X-ray studies, including tomography, demonstrated a local collapse of his left lung. Bacterial studies for tuberculosis were negative, and he was treated with antibiotics. After decreasing the dosage of BUC, his nail changes improved slightly, and other nail separations have not occurred. Examinations of nails and skin for fungi were negative. The localized pulmonary atelectasis has continued, but other adverse effects of BUC were not observed. He was free from edema and his serum immunoglobulin levels remained within the normal range.

CLINICAL FEATURES OF RA PATIENTS WITH YNS

In the literature, eleven RA patients with YNS have been reported (1, 2, 3, 5, 10). Profiles of these patients, plus those of our 2 patients, are summarized in Table 1.

In nine of the 11 patients reported in the literature, nail changes were considered to have been induced by drugs, D-Pen (4 patients) or BUC (5 patients). As was the case with our patients, the nail changes improved or completely disappeared in all the patients being treated with D-Pen or BUC after termination of medication, except for two patients whose details were not described. These observations convincingly confirm that the drugs were responsible for the nail changes observed in these patients.

In two (Nos 1 and 5) of the 13 RA patients, however, YNS was not associated with either D-Pen or BUC treatment (5, 10). The YNS symptoms were improved by rest in one patient, but remained unchanged in the other.

Interestingly, various complications, other than nail changes, were observed in 10 of the 13 patients, including those with drug-induced YNS: pulmonary complications, edema, and sinusitis were associated with 8, 5 and 2 of the patients, respectively. Three patients had proteinuria, and one patient had an IgA deficiency. One patient with spontaneous YNS had a pulmonary infarction, pleural effusions and lymphoedema of the legs; another had pulmonary fibrosis, chronic sinusitis and lymphoedema of the legs.

The systemic complications observed in a few RA patients with drug-induced nail changes can be explained by the well-known adverse effects of these drugs: edema with proteinuria, infections associated with IgA deficiency, and thrombocytopenia (1, 2, 5). Furthermore, nail changes disappeared after stopping medication, but improvement of the other complications were not always observed in the patients with YNS, including one of our patients. Therefore, the two events, nail changes and other complications, were considered to be induced by
different causes in most of the patients. In addition, we have observed seven RA patients who developed edema of extremities, but none of them had nail changes comparable to those observed in individuals with YNS. Nevertheless, we cannot exclude the possibility that the adverse effects of the drugs on nail growth might be augmented in the presence of pulmonary disease or edematous conditions. RA patients exhibiting nail changes during treatment with D-Pen or BUC should be carefully monitored for signs of systemic complications. It is also important to consider that mild changes in nails induced by the drugs might be overlooked by

Table 1 Profiles of rheumatoid arthritis patients associated with yellow nail syndrome

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Drug</th>
<th>Complications</th>
<th>Outcome of nail changes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharvill (1966)</td>
<td>1</td>
<td>?</td>
<td>F</td>
<td>Gold</td>
<td>pulmonary infarction, pleural effusion, leg edema</td>
<td>improved by rest</td>
<td>(10)</td>
</tr>
<tr>
<td>Lubach (1979)</td>
<td>2</td>
<td>33</td>
<td>F</td>
<td>D-Pen</td>
<td>sinusitis, bronchitis</td>
<td>improved*</td>
<td>(3)</td>
</tr>
<tr>
<td>Mattingly (1979)</td>
<td>3</td>
<td>30</td>
<td>F</td>
<td>D-Pen</td>
<td>pneumonia, pleural effusion, leg edema, IgA deficiency, proteinuria</td>
<td>?*</td>
<td>(5)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>59</td>
<td>M</td>
<td>D-Pen</td>
<td>pulmonary fibrosis, pleural effusion, atelectasis, thrombocytopenia</td>
<td>improved*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>56</td>
<td>M</td>
<td>none</td>
<td>pulmonary fibrosis, sinusitis, leg edema</td>
<td>unchanged</td>
<td></td>
</tr>
<tr>
<td>Ilchyshyn (1983)</td>
<td>6</td>
<td>26</td>
<td>F</td>
<td>D-Pen</td>
<td>proteinuria, microhematuria</td>
<td>improved*</td>
<td>(1)</td>
</tr>
<tr>
<td>Kikuchi (1990)</td>
<td>7</td>
<td>40</td>
<td>M</td>
<td>BUC</td>
<td>none</td>
<td>improved*</td>
<td>(2)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>46</td>
<td>F</td>
<td>BUC</td>
<td>pneumonia, pleural effusion, facial edema, hepatitis</td>
<td>improved*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>67</td>
<td>F</td>
<td>BUC</td>
<td>none</td>
<td>improved*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>39</td>
<td>F</td>
<td>BUC</td>
<td>none</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>42</td>
<td>F</td>
<td>BUC</td>
<td>proteinuria, hypoproteinemia, leg edema</td>
<td>improved*</td>
<td></td>
</tr>
<tr>
<td>Ichikawa (1991)</td>
<td>12</td>
<td>49</td>
<td>F</td>
<td>BUC</td>
<td>bronchitis</td>
<td>improved*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>45</td>
<td>M</td>
<td>BUC</td>
<td>atelectasis</td>
<td>improved**</td>
<td></td>
</tr>
</tbody>
</table>

F = female, M = male, Gold = gold sodium thiomalate, D-Pen = D-penicillamine, BUC = bucillamine. Nail changes after stopping treatment (*) or decreasing daily dosage (**).
both physicians and patients if the other complications were not present.

SERUM AND NAIL ELEMENTS IN RA PATIENTS

BUC (N-(2-mercapto-2-methylpropionyl)-L-cysteine) has a chemical structure which resembles that of D-Pen (dimethylcysteine): both SAARDs are derivatives of cysteine (Figure 6). Two cysteine molecules form cystine, from which a major component of nails, keratin, is synthesized.

The color and changes in shape of nails are sometimes induced by the accumulation of metals such as iron (Fe), copper (Cu), and others, whereas deficiencies of certain metals, including Fe, can also produce nail changes (spoon nails). Other drugs, such as bleomycin, 5-fluorouracil and gold compounds, have also been shown to cause nail discolorations.

The SH- and NH2-residues within the D-Pen molecule are known to mediate chelating effects on metals. D-Pen and BUC, therefore, may cause deficiencies of certain nail elements and thereby induce nail changes. The amounts of inorganic elements, such as calcium (Ca), magnesium (Mg), sodium (Na), potassium (K), Fe, Cu and zinc (Zn), were determined in 12 RA patients; 7 receiving BUC (2 with YNS), and 5 not receiving BUC. The method was by atomic absorption, as described by Vellar (9). The mean total dosage of BUC was 83 ± 70 (9–213) g in the 7 RA patients. Eight healthy adults served as controls.

Among the nail constituents, the Cu content was significantly higher in the RA patients (BUC group: 14.1 ± 8.1 μg/g, p < 0.05; non-BUC group: 21.5 ± 12.3 μg/g, p < 0.05) than in the controls (2.7 ± 1.0 μg/g, Table 2). For the other nail elements, no significant differences were observed. Serum Fe levels were higher in the BUC group (4.4 ± 0.3 μg/ml) than in the non-BUC group (3.9 ± 0.1 μg/ml, p < 0.05). However, one of the BUC-patients was also receiving oral iron replacement therapy. The other serum elements did not show any differences between the two groups of patients.

The results indicate that nail element deficiencies did not exist in our patients with RA. Unexpectedly, we found that the Cu content in the nails was higher in RA patients than in healthy adults. However, the high Cu contents were not specific for YNS, and the levels were similar for the RA patients receiving and not receiving BUC treatment. Thus, our results seem to support the suggestion of Kikuchi et al. (2) that BUC and D-Pen, because of their structural similarity with cysteine might disturb nail

\[
\begin{align*}
\text{CH}_3 \\
\text{CH}_3-\text{C}-\text{CH}-\text{COOH} \\
\text{HS} \quad \text{NH}_2
\end{align*}
\]

D-penicillamine

(dimethylcysteine)

\[
\begin{align*}
\text{CH}_3 \\
\text{HS}-\text{CONHCH}-\text{COOH} \\
\text{CH}_3 \quad \text{CH}_2\text{-SH}
\end{align*}
\]

bucillamine

\[
\begin{align*}
\text{CH}_2\text{-CH}-\text{COOH} \\
\text{S} \quad \text{NH}_2
\end{align*}
\]

cysteine

\[
\begin{align*}
\text{CH}_2\text{-CH}-\text{COOH} \\
\text{S} \quad \text{NH}_2
\end{align*}
\]

cystine

\[
\begin{align*}
\text{CH}_2\text{-CH}-\text{COOH} \\
\text{NH}_2
\end{align*}
\]

keratin

Fig. 6. Chemical structures of D-penicillamine and bucillamine, and their association with cysteine, cystine and keratin.
Table 2  Contents of inorganic elements in the nails and sera of patients with rheumatoid arthritis

<table>
<thead>
<tr>
<th></th>
<th>Ca</th>
<th>Mg</th>
<th>Na</th>
<th>K</th>
<th>Fe</th>
<th>Cu</th>
<th>Zn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nails (µg/g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUC (n = 6)</td>
<td>271</td>
<td>124</td>
<td>797</td>
<td>248</td>
<td>54</td>
<td>14.1</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>±164</td>
<td>±97</td>
<td>±411</td>
<td>±251</td>
<td>±34</td>
<td>±8.1</td>
<td>±55</td>
</tr>
<tr>
<td>Non-BUC (n = 3)</td>
<td>150</td>
<td>83</td>
<td>806</td>
<td>175</td>
<td>77</td>
<td>21.5</td>
<td>139</td>
</tr>
<tr>
<td>Controls (n = 6)</td>
<td>±15</td>
<td>±10</td>
<td>±312</td>
<td>±45</td>
<td>±47</td>
<td>±12.3</td>
<td>±28</td>
</tr>
<tr>
<td>Serum (µg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUC (n = 5)</td>
<td>84.3</td>
<td>18.6</td>
<td>2354</td>
<td>145</td>
<td>4.4</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>±1.2</td>
<td>±1.3</td>
<td>±125</td>
<td>±16</td>
<td>±0.3</td>
<td>±0.1</td>
<td>±0.1</td>
</tr>
<tr>
<td>Non-BUC (n = 5)</td>
<td>82.0</td>
<td>18.8</td>
<td>2238</td>
<td>164</td>
<td>3.9*</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>±3.8</td>
<td>±0.8</td>
<td>±58</td>
<td>±7</td>
<td>±0.1</td>
<td>±0.2</td>
<td>±0.1</td>
</tr>
</tbody>
</table>

Inorganic elements in nails or sera from patients with rheumatoid arthritis receiving bucillamine (BUC), or other treatment (non-BUC), and healthy adults (controls). Determinations were by atomic absorption. Data presented as means ± one standard deviation.

growth through on inhibition of keratin synthesis.

To further clarify the association between nail changes and other systemic complications in both spontaneous and drug-induced YNS, more patients with YNS must be analyzed. The determinations of serum amino acid levels, including cysteine and cystine, appear to be necessary in patients with drug-induced YNS.

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