

# Adhesive capsulitis of the shoulder in human immunodeficiency virus-positive patients during highly active antiretroviral therapy

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Many adverse events have been described in patients treated with highly active antiretroviral therapy (HAART). Recently, among these, adhesive capsulitis of the shoulder has been described in some patients using protease inhibitors. We report our experience with 6 human immunodeficiency virus-positive patients in whom adhesive capsulitis of the shoulder developed during HAART. All 6 patients were treated with the same antiretroviral drug combination (HAART) including nucleoside reverse transcriptase (stavudine and lamivudine) and protease inhibitors (indinavir). The clinical pattern of adhesive capsulitis during HAART is similar to the classical form of adhesive capsulitis. Examining our case studies, we postulate a correlation between HAART and adhesive capsulitis. Discontinuation or reduction of the dosage of protease inhibitors associated with conventional conservative treatment is effective in reducing the symptoms and resolving the disease. (*J Shoulder Elbow Surg* 2006;15:188-190.)

In the last several years, protease inhibitors have had a dramatic effect on the prognosis of human immunodeficiency virus (HIV) infection. Highly active antiretroviral therapy (HAART) is usually effective in reducing plasma HIV-ribonucleic acid (RNA) levels (ie, viral load), accompanied by a gradual increase in CD4 cell counts, sometimes to the normal level. However, many adverse events are associated with the use of HAART, including hyperlipidemia, diabetes mellitus, and lipodystrophy.<sup>13</sup> Recognition and effective treatment of these adverse effects are becoming

more important along with the increasing duration and efficacy of antiretroviral therapy.

Adhesive capsulitis of the shoulder, a clinical entity characterized by progressive stiffness of the glenohumeral joint and articular pain,<sup>6</sup> is not yet recognized as a common adverse event of HAART. However, 19 cases of adhesive capsulitis of the shoulder occurring in patients with HIV receiving HAART have been reported in the literature.<sup>4,5,7,10,11,14</sup> It has been suggested that protease inhibitors might be responsible for the index event.<sup>4,5,7,10,11,14</sup>

This report details our experience with 6 HIV-positive patients in whom adhesive capsulitis of the shoulder developed during HAART.

## PATIENTS

Six patients (five men and one woman) with HIV-1 infection, receiving HAART, in whom adhesive capsulitis of the shoulder developed were identified at our institution between December 1997 and October 1999. The same pharmacologic treatment was routinely administered at our institution in about 50 patients among whom were the 6 cases we report herein. Our patients' status is summarized in Table I.

The diagnosis of HIV infection had been made between 1985 and 1998. All of the patients were ranked according to the 1993 revised Centers for Disease Control and Prevention HIV classification system.<sup>9</sup> Four patients had a diagnosis of acquired immune deficiency syndrome that was defined on the basis of opportunistic infections occurring in their past history: two had had a progressive multifocal leukoencephalitis, one had a disseminated *Cytomegalovirus* infection, and one had a pulmonary tuberculosis infection in the past (>1 year previously). Two patients were in the symptomatic HIV-positive stage.

All 6 patients were treated with the same antiretroviral drug combination (HAART) including nucleoside reverse transcriptase (stavudine and lamivudine) and protease inhibitors (indinavir). More specifically, the treatment consisted of indinavir (800 mg 3 times daily), stavudine (40 mg twice daily), and lamivudine (150 mg twice daily) for a period ranging from 3 to 24 months. In 3 patients, the treatment was effective, with a negative HIV-RNA level (copies per milliliter) under the detectable limit and an increase in the number of circulating CD4<sup>+</sup> lymphocytes (mean CD4 cell count at onset of adhesive capsulitis pain of

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**Table I** Population demographics and clinical status

	Patient No.					
	1	2	3	4	5	6
Sex	M	M	M	F	M	M
Age (y)	41	35	56	42	43	43
Occupational status	Businessman	Unemployed	Doorman	Housewife	Unemployed	Unemployed
Risk factor	Heterosexual	Heterosexual	Bisexual	Heterosexual	Heterosexual	Exdrug user
Year of HIV-1 infection diagnosis	1985	1998	1996	1989	1997	1998
CDC	C3	B2	B2	C3	C1	C3
CD4	254	>499	382	5	1050	116
VL	<80	<80	4400	750	<80	5700
Affected shoulder	Right	Right	Bilateral	Right	Bilateral	Right
Date of HAART commencement	December 1997	March 1999	March 1998	July 1997	October 1999	June 1998
Date of adhesive capsulitis onset	May 1999	May 1999	May 1999	December 1997	October 1999	September 1998
Time span (mo)*	17	2	14	5	24	3
Antiretroviral therapy change	No	Yes	No	Yes	Yes	No

CDC, Stage of HIV infection according to Centers for Disease Control and Prevention classification<sup>9</sup>; CD4, number of CD4 cells/ $\mu$ L; VL, HIV-RNA in plasma detected with nucleic acid sequence-based amplification system (copies/mL).

\*Time between HAART commencement and adhesive capsulitis onset.

384 cell/ $\mu$ L). Two patients had been treated with phenobarbital: one for 6 months and the other one for 9 months before the appearance of shoulder pain. No other classic causes of frozen shoulder (trauma, disorders involving mediastinal organs such as myocardial infarction, pericarditis, or pneumothorax, neurologic disorders such as coma, hemiplegia, or Parkinson's disease, use of isoniazide or ethionamide, and so on) were present.

In all of the patients, a classic frozen shoulder syndrome developed during HAART.<sup>8</sup> The mean time span between the beginning of therapy and the onset of adhesive capsulitis was 11 months (minimum, 2 months, maximum, 24 months). The diagnosis of adhesive capsulitis of the shoulder was based on clinical features,<sup>6</sup> including shoulder pain and motion restriction lasting for at least 1 month in the absence of a history of significant trauma or surgical procedures. The onset of the clinical picture was progressive over a few weeks. The initial clinical picture was characterized by pain, and this brought the patients to our attention.

In a second phase, the pain lessened but was followed by a reduction in range of active and passive motion in all directions (>20% in external rotation, >70% in flexion, and >70% in true abduction). In 2 cases, the adhesive capsulitis was bilateral; in 1 case, the most affected side was the left, and in the other, it was the right. There were no clinical or radiographic signs of subacromial bursitis, glenohumeral osteoarthritis, or osteonecrosis of the humeral head. The radiographic examination of the shoulder showed a normal glenohumeral joint and normal subacromial space. Bone stock showed no signs of demineralization, and no periarticular calcium deposits were observed. All of the patients were examined by arthrography, which confirmed the diagnosis based on clinical findings. The examination showed reduction in the joint capacity, with a feeling of a tight joint at the introduction of the contrast medium.

All of the patients underwent specific conservative treat-

ment for frozen shoulder consisting of physical therapy (active and passive range-of-motion exercises, cryotherapy, electroanalgesia [transcutaneous electrical nerve stimulation]), nonsteroidal anti-inflammatory drugs, and analgesics. Three patients modified the antiretroviral therapy after the onset of adhesive capsulitis, interrupted the drug's delivery, and they experienced spontaneous recovery at a mean of 2 to 4 months. Three patients did not modify the therapy. One of them recovered spontaneously at 6 months, one had a partial reduction of symptoms, and the last one dropped out of the study.

## DISCUSSION

Adhesive capsulitis of the shoulder is a condition of unknown etiology, characterized by a painful restriction of passive and active motion of the glenohumeral joint, with a progressive contraction of the joint capsule,<sup>6,7</sup> in the absence of degenerative joint disease. Secondary frozen shoulder occurs in association with specific disorders or precipitating events. In our patients, the onset of adhesive capsulitis could not be related to any known systemic disease or predisposing factor. The HIV infection itself is not recognized as a predisposing condition.<sup>5</sup> Only 2 patients had been taking phenobarbital, a drug potentially related to shoulder disease, for a long time (8 and 12 months, respectively), but we observed the onset of adhesive capsulitis only after the administration of HAART.

In the absence of any other known condition associated with secondary adhesive capsulitis, we postulate a correlation between HAART and adhesive capsulitis. All of our HIV-positive patients received the same antiretroviral therapy, including stavudine, lamivudine, and indi-

navir. Some indirect evidence, however, suggests a possible correlation with protease inhibitors, such as indinavir, in the pathogenesis of adhesive capsulitis. In fact, on the basis of the literature data, this complication has never been described in patients treated with stavudine plus lamivudine alone. Instead, the association of the 3 drugs (indinavir, stavudine, and lamivudine) was always present in all of the cases described previously,<sup>5,7,10,11,14</sup> and the number of reported cases seems sufficient to rule out a coincidental association. At the moment, considering indinavir as the only cause of adhesive capsulitis might be too simplistic. In fact, at our institution, several protease inhibitors, such as ritonavir, amprenavir, lopinavir, and saquinavir, are routinely used, and we have observed no case of adhesive capsulitis in patients treated with these drugs. However, recently, one report described a case of adhesive capsulitis in a patient taking nelfinavir, which is a different protease inhibitor.<sup>4</sup> This observation induced the authors to indicate a probable pathogenic class effect of protease inhibitors rather than a specific toxicity of indinavir.<sup>4</sup>

The pathologic mechanism by which indinavir might cause adhesive capsulitis is difficult to hypothesize. Bunker and Anthony<sup>1</sup> described the pathologic features of adhesive capsulitis as a fibrosing condition with active fibroblastic proliferation, which are identical to the ones observed in fibromatoses, such as Dupuytren's disease of the hand. Transforming growth factor  $\beta$  (TGF- $\beta$ ) is a key cytokine in all fibrosing syndromes. It causes excessive deposition of extracellular matrix protein, and it also increases the production of protease inhibitors of the matrix, blocking matrix degradation.<sup>6</sup> Rodeo et al<sup>12</sup> found that the frequency of cytokines, such as TGF- $\beta$  and platelet-derived growth factor, is greater in capsular biopsy specimens from patients affected by primary or secondary adhesive capsulitis. More recently, an altered expression pattern of growth factors, cytokines, and matrix metalloproteinases in frozen shoulder was confirmed.<sup>2</sup> Although we do not have any direct evidence, we can postulate that the pathologic mechanism involved could be the inhibition of the matrix degeneration mediated by TGF- $\beta$ . The starting event could be a precipitation of the drug in the joint,<sup>7,10</sup> in the same manner as what occurs in the kidney.<sup>3,13</sup> In fact, Zabraniecki et al<sup>14</sup> reported that indinavir was found in joint fluid samples taken before arthrography in 2 patients.

Although some authors propose surgical treatment for adhesive capsulitis,<sup>6</sup> we administered only conservative treatment. This was because of some obvious concern about the general status of our patients, which suggested a more conservative approach. In fact, at the time of our first observations, the prognosis and general conditions of these patients were much worse than at present. In a certain way, the unexpected, spontaneous trend to resolution made any more aggressive treatment

unnecessary. The more rapid clinical course of adhesive capsulitis in these patients, with respect to the classic form, was another element that persuaded us to avoid surgical treatment.

In conclusion, our experience induces us to propose the inclusion of HAART with indinavir among the possible causes of secondary adhesive capsulitis. We cannot establish whether the onset of adhesive capsulitis is to be ascribed only to indinavir or if other factors are implicated, such as the association with stavudine and lamivudine. Other studies are necessary to determine better the correlation between HAART including indinavir or other protease inhibitors and the onset of adhesive capsulitis. Discontinuation or reduction of the dosage of protease inhibitors associated with conventional conservative treatment is effective in reducing the symptoms and resolving the disease.

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