FROZEN SHOULDER: A NEW DELAYED COMPLICATION OF PROTEASE INHIBITOR THERAPY?*

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SUMMARY. - We report three cases of frozen shoulder (including one with bilateral involvement) in human immunodeficiency virus (HIV)-positive patients under triple antiretroviral therapy. In each case, the diagnosis was confirmed by arthrography, and the classic causes of frozen shoulder were ruled out. We suggest that protease inhibitor therapy may have contributed to the development of frozen shoulder in these patients. Long-term follow-up of the increasing numbers of patients under triple antiretroviral therapy will confirm or refute this hypothesis.

Key words: **Shoulder - Frozen shoulder - HIV - Triple therapy - Protease inhibitor.**

RÉSUMÉ. - *Rétraction capsulaire de l'épaule : une nouvelle complication tardive des antiprotéases ?* - Les auteurs rapportent 3 observations de rétraction capsulaire de l'épaule (dont une bilatérale) chez des patients séropositifs pour le VIH traités par trithérapie anti-rétrovirale. Le diagnostic a été chaque fois confirmé par une arthrographie et les causes classiques de rétraction capsulaire ont été éliminées. Nous mettons en avant le rôle iatrogénique joué par les anti-protéases, étant entendu que seul le suivi au long cours de patients toujours plus nombreux à utiliser la trithérapie pourra apporter une réponse définitive.

Mots clés : **Épaule - Capsulite rétractile - VIH - Trithérapie - Anti-protéase.**

The advent of protease inhibitors two years ago was a breakthrough in the treatment of HIV infection. The use of these promising drugs has increased steadily, and so has the number of their reported side effects. We report three cases of frozen shoulder in patients receiving triple antiretroviral therapy for HIV infection.

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Case-reports

Case 1

This 56-year-old right-handed homemaker was referred to our department in 1997 for pain in her right shoulder. She had been found to be seropositive for the HIV in 1989 and had been taking three antiretroviral drugs (Zerit®, Epivir®, and Crixivan®) for the last year. Five months before her referral, she developed herpes zoster in the distribution of C5. She recovered from the episode, but since then suffered from pain in her right shoulder. Physical findings were muscle wasting about the right shoulder and restriction of the range of active and passive motion of the joint (abduction and external rotation of the glenohumeral joint, 30° and 5°, respectively). Constant's functional score (without power measurements) was 8/75. Comparative plain radiographs of the shoulders showed that the glenohumeral joint space and contours of the humeral head were normal and that there was no noticeable demineralization. During arthrography, no fluid was obtained, and only 8 ml of contrast medium could be injected into the joint. The capacity of the joint cavity was reduced, especially in the area of the subscapular recess. Moderate unevenness of the synovial membrane was seen. There were no other abnormalities. The synovial recesses ruptured at the end of the injection, and a cor-

ticosteroid was injected. The patient had none of the classic risk factors for frozen shoulder. Laboratory tests showed a three-fold increase in the serum TSH level with normal thyroid hormone levels. The ECG and chest film were unremarkable. The outcome was favorable after a two-month program of aggressive physical therapy.

Case 2

A 46-year-old right-handed laundrywoman known to be seropositive for the HIV since 1989 started experiencing pain and motion restriction in her left shoulder in March 1997, one year after starting therapy with three antiretroviral drugs (Zerit®, Epivir®, Crixivan®). Her symptoms worsened gradually, and she was admitted to our department in July 1997. Active and passive motion of the left shoulder was restricted (25° abduction and 0° external rotation of the glenohumeral joint). The other physical findings were normal. Constant's score (without power measurements) was 26/75. On comparative radiographs of the shoulders, the glenohumeral joint space and subacromial space were normal, the bone was not demineralized, and there were no periarticular calcium deposits. Increased resistance to injection was noted during arthrography, and only 10 ml of Hexabrix® could be injected. The only abnormality was a reduction in the capacity of the joint. The synovial recesses ruptured, and a corticosteroid was injected. No risk factors for frozen shoulder were found by history or physical examination. The serum glucose profile, tests for inflammation, and tests for thyroid function were normal. The ECG was normal apart from inversion of the T waves in aVR and V1. The chest film was unremarkable. The outcome was favorable after aggressive physical therapy, but the patient currently has similar symptoms in her other shoulder.

Case 3

A 47-year-old man who was found to be seropositive for the HIV in 1985 and had been taking three antiretroviral drugs for the last 14 months (Zerit®, Epivir®, Crixivan®) came to our clinic for a three-month history of pain in his right shoulder. Active and passive abduction and internal rotation of the joint were restricted. No joint abnormalities or demineralization were seen on the comparative radiographs of the shoulders. During arthrography, the joint felt tight to injection, and the volume injected (Hexabrix®) was only 10 ml. The synovial recesses ruptured. No other abnormalities were seen. A corticosteroid was injected. A medical history, a physical examination, laboratory tests (including serum glucose and TSH levels and tests for inflammation), an ECG, and a chest film failed to detect any of the classic risk factors for frozen shoulder. The outcome was favorable under aggressive physiotherapy.

Discussion

We suggest that protease inhibitor therapy contributed to the development of frozen shoulder in our three patients. The diagnosis of frozen shoulder was documented by an arthrography. A thorough workup including a medical history, a physical examination, and appropriate laboratory tests failed to find any evidence of the classic causes of frozen shoulder, namely injury to the shoulder; disorders involving a mediastinal organ (myocardial infarction, pericarditis, pneumothorax); neurologic disorders (coma, hemiplegia, Parkinson's disease); use of isoniazid, ethionamide, phenobarbital, or iodine 131; incipient inflammatory joint disease; infectious capsulitis; diabetes mellitus; and hyperthyroidism [1-8]. Our first patient had mild compensated hypothyroidism, which did not require treatment, and a history of herpes zoster; for neither of these two conditions has any association with frozen shoulder been reported. Although idiopathic frozen shoulder accounts for 50% of all cases of this disorder [1,4,6,7], the fact that our three patients had HIV infection treated by three antiretroviral agents militates against this diagnosis. HIV infection can cause a number of neurologic disorders, either directly or via the occurrence of opportunistic infections; however, no association between frozen shoulder and HIV infection has been reported to date. Also, the absence of radiographic demineralization in our three patients and the involvement of both shoulders in one patient are consistent with drug-induced frozen shoulder [3,5]. The limited clinical experience available with protease inhibitors, which were introduced only two years ago, suggests that frozen shoulder may be an as yet unreported side effect of protease inhibitor therapy.

Protease inhibitors were recently introduced for the treatment of HIV infection, in combination with nucleoside analogues, an older class of antiretroviral agents formerly used as single drug therapy. Dideoxynucleoside analogues (AZT or Retrovir®, ddi or Videx®, ddC or Zerit®, 3TC or Epivir®) competitively inhibit the enzyme reverse transcriptase. They stop the production of DNA complementary to the viral RNA, and therefore prevent the virus from infecting new cells. However, they have no effect on the provirus already incorporated into the cell genome. Also, the duration of their effect is limited because after some time mutations occur in the reverse transcriptase gene. Dideoxynucleoside analogs also inhibit the mitochondrial DNA polymerases of the host cell, thereby causing a number of unwanted gastrointestinal, hematologic, and above all neuromuscular effects [10,11].

Protease inhibitors interfere with assembly of the viral proteins produced by translation of the proviral DNA incorporated into the host cell genome. The HIV protease is the enzyme that ensures maturation of the viral particles. Protease inhibitors lead to the production of nonfunctioning viral particles, and also decrease viral replication in infected cells. Protease inhibitor therapy is responsible for a dramatic drop in viral burden and for an increase in CD4+ counts. Here again, however, mutations affecting the HIV protease can cause resistance. The current strategy for decreasing the risk of treatment resistance is administration of a combination of two nucleoside analogies and one protease inhibitor.

Four protease inhibitors are currently used in France, saquinavir (Invirase®), ritonavir (Norvir®), indinavir (Crixivan®), and nelfinavir

(Viracept®, approved temporarily). Our three patients were all under indinavir, but this drug is the protease inhibitor most widely used in France. Adverse effects of indinavir reported to date are nausea (35%), headache (25%), diarrhea (25%), asthenia (25%), rash (19%), taste perversion (19%), dry skin (16%), urinary tract lithiasis (4%), liver function test abnormalities, myalgia (5%), pruritus (7%), hyperesthesia (7%) and paresthesia (5%). The last two manifestations may indicate peripheral neuropathy. These adverse effects occur early after initiation of the drug, whereas in our patients about 12 months elapsed before the development of frozen shoulder. This long time interval makes it difficult to establish causality but is consistent with descriptions of frozen shoulder induced by other drugs [5].

Protease inhibitors share with phenobarbital and isoniazid the ability to competitively inhibit cytochrome P450. This leads to numerous side effects and can increase the toxicity of concomitant drugs [3,9].

The pathophysiology of frozen shoulder is obscure. Protease inhibitors may cause frozen shoulder via a direct mechanism involving (a) a peripheral neuropathy (one of the many pathogenic hypotheses put forward for frozen shoulder involves autonomic nervous system abnormalities); (b) thyroid dysfunction (thyroid follicle cell hypertrophy has been found in rats treated with protease inhibitors); (c) and/or alterations in glucose metabolism (a few cases of diabetes mellitus have been reported in patients receiving protease inhibitor therapy) [12]. Alternatively, protease inhibitors may cause frozen shoulder via an indirect mechanism, such as potentiation of the neurotoxicity of nucleoside analogues. It remains to be determined whether frozen shoulder is a class effect or occurs only with indinavir.

Conclusion

Our three case-reports suggest that protease inhibitor therapy may be capable of inducing frozen shoulder after several months. Further experience including long-term follow-up of patients under protease inhibitor therapy is needed to confirm or refute this hypothesis.

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