

## Osteonecrosis in Inflammatory Bowel Diseases : a review of the literature

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### Abstract

**Introduction :** Osteonecrosis (ON) of the femoral head can lead to femoral head collapse, necessitating total hip replacement. Reports of patients suffering from both ON and Inflammatory Bowel Diseases (IBD) have prompted us to evaluate the relationship between ON and IBD, especially Crohn's disease and ulcerative colitis.

**Methods :** A review of the data from three new cases, along with data from all the published cases of patients presenting ON and IBD found through a systematic search of the Pub Med database.

**Results :** We encountered some diagnostic problems : The ON diagnosis could not be confirmed in some patients who did not meet the ON diagnostic criteria. Reviewed data was too weak to assess the exact incidence of ON in IBD. Corticosteroid therapy, especially in high dose regimens, is likely the most important etiological factor. No evidence supporting other physiopathological hypothesis, such as total parenteral nutrition, osteoporosis, or coagulation disorders, was found. Finally, the multifocal form of ON appears particularly common in IBD, with some patients presenting multiple lesions of the hip, shoulder, knee and talus.

**Conclusions :** ON in IBD, which is frequently multifocal, appears to be a complication of corticosteroid therapy, especially when high doses are used. We recommend regular ON checkups for corticosteroid-treated IBD patients. (*Acta gastroenterol. belg.*, 2009, 72, 327-334).

**Key words :** osteonecrosis, inflammatory bowel diseases, Crohn's disease, ulcerative colitis, corticosteroids.

### Introduction

Crohn's disease and ulcerative colitis are the most common forms of inflammatory bowel disease (IBD). Three cases of osteonecrosis (ON) in patients suffering from IBD prompted us to review the literature for all the published cases and evaluate the relationship between both diseases.

Osteonecrosis is characterized by bone infarct in the subchondral area, particularly the femoral head. This may cause a collapse of the subchondral bone, likely leading to severe hip osteoarthritis. ON may also affect other joints, including the shoulder (humeral head), knee (femoral or tibial components), and ankle (talus or tibia). Some etiological factors have been identified, e.g. traumas like fracture or dislocation, sickle cell and Gaucher's diseases, corticotherapy, alcohol consumption, and radiotherapy. In aseptic non-traumatic cases, the pathogenic process remains unknown. There are currently no clinical diagnostic criteria for ON, though pain is the most common symptom. However, pain is not specific, and as ON can be completely asymptomatic, it may not even be present (1). ON diagnosis is therefore based on

other methods. Radiological criteria such as the collapse of the subchondral bone and trabecular bone remodeling with a normal acetabulum and articular space, were the first employed (2). In the early stages, prior to radiological modifications, histopathologic core biopsy criteria can be applied, and include bone marrow necrosis and the presence of dead osteocytes in at least 50% of osteocyte lacunae (3). Since 1984, MRI studies have proven very valid, and are replacing core biopsy (4). MRI diagnostic criteria include an area of normal T1 or hyposignal T1 surrounded by a hypo T1 line (4,5). On T2 sequence, this line can become a "double line" composed of a hyper-signal on a hypo-signal line (5). Such a double line sign seems the most specific criteria but is not constantly found. In one published series, only 34% showed the double line sign (6). Bone scintigraphy is of little interest, as it is neither sensitive (23% false positives) nor specific (20% false positives) (4).

### Methods

We collected the data of three new ON in IBD cases, and reviewed the data of published cases using the Pub Med database. The keywords used were osteonecrosis, bone necrosis, Crohn, ulcerative colitis, and inflammatory bowel disease. The data we collected from our 3 cases was added.

ON was diagnosed based on radiological criteria (subchondral bone collapse and trabecular bone remodeling with a normal acetabulum and a normal articular space), MRI criteria (an area of normal T1 or hypo-signal surrounded by a hypo T1 line, and a "double line" on T2 sequence), or pathological criteria (bone marrow necrosis and the presence of dead osteocytes in at least 50% of osteocyte lacunae).

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## Results

### *Review of the published cases of ON in IBD*

The literature review yielded a total of 56 reported ON cases (7-21). The diagnostic criteria were verified in each case. In eight of these cases, the diagnosis was made without x-ray or MRI confirmation, despite clinical presentations suggesting other diagnoses: three cases presented possible ankylosing spondylitis, three cases showed a positive bone scintigraphy without confirmation from x-ray, MRI, or biopsy, one MRI study case showed a regressive edema suggestive of transient osteoporosis, and another case presented dissecans osteochondritis with loose bodies in the knee. We excluded these eight cases (Table 2) from the analysis and used only the 48 validated cases (Table 1).

### *Characteristics of ON in IBD*

The data from the new and already published cases was pooled. The results are presented in Table 1.

The patients' mean age was 31 years (14-49), and there was no predominant gender (28 males/23 females). The femoral head was the most frequently involved site (40/51), followed by the knee (20/51). Multifocal lesions were present in 23/43 ON cases, 91% of which had a history of corticosteroid (CS) therapy.

### *Frequency of ON in IBD*

In a series of 20 cases of refractory IBD with long-term CS therapy, a systematic and prospective MRI study of the hips revealed 5 ON cases (21).

Two retrospective reviews have been published (9, 18). In the first series, which included 161 IBD cases, 7 ON cases were diagnosed (9). However, two of these diagnoses did not fulfill the diagnostic criteria, as they were based only on a positive bone scintigraphy unconfirmed by x-rays, histopathology, or MRI (Table 2).

In the second retrospective series, including 877 patients followed up for 20 years in a Crohn's clinical referral practice (16), four cases were diagnosed. Again, two of these cases failed to fulfill ON diagnostic criteria and were excluded from analysis (Table 2).

Based on these data reviews, the frequency of ON in IBD can be estimated at 0.17% to 2.6%, and 25% in refractory IBD with long-term CS therapy.

### *Relationships between ON in IBD and corticosteroid therapy (Table 1)*

Corticosteroids were used in 50/51 ON cases. When CS therapy details were available, most patients were found to have received high doses (more than 30 mg of prednisone per day), at least at the start of the treatment. Intravenous therapies were common (14/22), and the cumulative dosage averaged 9.75 g of prednisone (1.8-19.9). Treatment duration varied from 1.1 to 120 months (mean 18.8). Joint pain was occasionally reported (8/19),

typically during the first month of CS therapy, and in some cases disappeared several months before ON diagnosis. The mean delay between onset of CS therapy and ON diagnosis was 117 months (2 days-504 months), but 8/32 patients were diagnosed during their first year of CS therapy. The diagnosis delay was 1 month or less in three cases.

### *ON in IBD and total parenteral nutrition (Table 1)*

In our review, data pertaining to total parental nutrition was available for 15 ON cases, eight of which used total parental nutrition. All these patients also received high doses of corticosteroids.

### *ON in IBD and osteoporosis (Table 1)*

In our review, only six case reports contained bone mineral density values, which were all normal. Two of our three cases presented osteoporosis.

### *ON in IBD and coagulation disorders (Table 1)*

Coagulation factors were determined in six cases. In one case, increased serum levels of factor VIII, tissue plasminogen activator antigen, lipoprotein A, and homocysteine were reported (18).

## Discussion

The absence of consistent data on ON in IBD due to incomplete reports, poorly described diagnostic criteria, and lack of differential diagnoses, is immediately obvious. For joint pain in IBD patients, differential diagnoses include arthritis with or without spondylitis, transient osteoporosis of the hip with or without stress fractures, and osteoarthritis (unusual in young people). Our review frequently encountered poorly defined diagnostic criteria and the absence of differential diagnosis discussion. ON in IBD occurs primarily in the young, as is the case with IBD onset (15-35 years) (22). There was no gender predominance. Repartition of the most frequently involved sites (hip and knee) is typical of non-traumatic ON (23). The multifocal presentation of ON seems very frequent (53.5%) in IBD, and the frequency of multifocal lesions might have been higher had a systematic total body MRI evaluation been performed on each patient to detect asymptomatic ON lesions. Such a high frequency of multifocal lesions should be compared to the estimated incidence in non-traumatic ON unrelated to IBD. In a retrospective multicenter study, non-traumatic ON cases were multifocal in only 3.3% (24). Such a high level of multifocal ON in IBD patients merits further investigation.

We believe that the literature is not a sufficient basis for a realistic evaluation of the incidence of ON in IBD. Of the three studies we found, the only systematic prospective study of ON in IBD was published in 2007 by Kamata *et al.* (21). The series was limited to "refrac-

Table 1. — ON in IBD : three new cases and published cases

UC = ulcerative colitis. Ch = Crohn's disease. Ref = references of the article. Gender : M = male and F = female. Y = yes. N = normal. No = no. Pain onset and delay after corticosteroid treatment in months. Multifocal = more than 2 sites. Sites of ON (= osteonecrosis) : H = hip, K = knee, S = shoulder. Diagnostic tool : Xr = radiography, Scinti = scintigraphy. Mean daily dose and range in mg prednisone. Cumulative dose in g prednisone. TPN = total parenteral nutrition. BMD = bone mineral density (by DEXA) : Op = osteoporosis (T-score  $\leq -2.5$ ), P = osteopenia (T-score between -1 and -2.5), SI = sacroiliac joint. CS = corticosteroids.

| Ref    | Case | Age | Gender | IBD | ON           |                         |            |                    |                 |               | Corticosteroids |                 |       |          |                 | TPN | BMD                                                                    | Remarks |
|--------|------|-----|--------|-----|--------------|-------------------------|------------|--------------------|-----------------|---------------|-----------------|-----------------|-------|----------|-----------------|-----|------------------------------------------------------------------------|---------|
|        |      |     |        |     | Pain onset   | Delay after start of CS | Multifocal | Sites of ON        | Diagnostic tool | IV            | Orally          |                 |       |          |                 |     |                                                                        |         |
|        |      |     |        |     |              |                         |            |                    |                 |               | Dose            | Mean daily dose | Range | Duration | Cumulative dose |     |                                                                        |         |
| case 1 |      | 21  | M      | UC  | ?            | 10                      | N          | H,H                |                 | MRI,Xr        | Y?              | Y               | ?     | 3        | ?               | Op  |                                                                        |         |
| case 2 |      | 36  | M      | Ch  | 0.8 (20d)    | 13                      | Y          | H,H,K,K            |                 | MRI,Xr        | No              | 48              | 40-64 | 2        | 2.32            | Op  | hemostasis study N                                                     |         |
| case 3 |      | 49  | M      | Ch  | 12           | 24                      | Y          | H,H,K,K,K,         |                 | MRI,Xr        | 120x15          | Y?              | 8-32  | 42       | >14             | No  | P                                                                      |         |
| 10     | 1    | 27  | F      | Ch  | 0.08 (2d)    | 0.08                    | ?          | s,s + ?            |                 | Xr            | No              | Y?              | ?-60  | 4        | >4              | No  | ?                                                                      |         |
| 11     | 1    | 16  | F      | Ch  | 4            | 7                       | Y          | K,both elbow,talus |                 | Xr            | Max 1.4/kg/d    | ?               | ?     | 1.3      | ?               | Y   | ?                                                                      |         |
| 11     | 2    | 14  | F      | Ch  | 1            | 6                       | N          | K,K                |                 | Xr            | Max 1.4/kg/d    | ?               | 4     | 1.5      | ?               | Y   | ?                                                                      |         |
| 11     | 3    | 16  | M      | Ch  | 0            |                         | Y          | H,H,K,K,talus      |                 | Xr,Scinti     | Max 1.0/kg/d    | ?               | ?     | 1,2      | ?               | Y   | No data for previous CS                                                |         |
| 12     | 1    | 29  | M      | UC  | 0.7 (3weeks) | 9                       | Y          | H,H,talus          |                 | Xr            | Y?              | 28              | ?-60  | 6        | 4.7             | No  | ?                                                                      |         |
| 12     | 2    | 30  | M      | Ch  | 1            | 2                       | Y          | H,H,S              |                 | Xr            | Y               | 26              | ?     | 16       | 13.5            | ?   | Previous CS                                                            |         |
| 12     | 3    | 26  | F      | UC  | 4.7          |                         | Y          | H,H,K              |                 | Xr            | ?               | 19              | ?-60  | 5.1      | 3               | ?   | Previous CS                                                            |         |
| 12     | 4    | 29  | F      | UC  | 15           | 15                      | N          | H,                 |                 | Xr            | No              | 17              | ?-30  | 4.4      | 2.4             | ?   | ?                                                                      |         |
| 13     | 1    | 46  | M      | Ch  | 12           | 12                      | N          | H,Lunate           |                 | Xr,Scinti     | No              | 7,5             |       | 2        | ?               | N   | ?                                                                      |         |
|        |      |     |        |     |              |                         |            |                    |                 |               |                 |                 |       |          |                 |     | Scinti + other hip, feet, left knee. Xr N but no MRI or follow up data |         |
| 14     | 1    | 27  | M      | Ch  | 6            | 6                       | Y          | H,H,K,K,           |                 | Xr,Scinti     | ?               | ?               | 10-60 | 6        | ?               | N   | ?                                                                      |         |
| 15     | 1    | 21  | M      | UC  | 1            | 30                      | Y          | K,K,Elbow          |                 | Xr            | No              | 80              | ?     | 7        | 8.6             | ?   | ?                                                                      |         |
| 18     | 1    | 34  | M      | UC  | 0.7          | 1                       | N          | K,K,               |                 | MRI,Xr,Scint  | 70              | ?               | ?     | ?        | ?               | Y   | P                                                                      |         |
|        | 2    | 25  | F      | Ch  | 18           |                         | N          | K,K                |                 | MRI,Xr        | 60              | 60              | ?     | ?        | 300             | No  | P                                                                      |         |
| 19     | 1    | 28  | M      | Ch  | 0.7          | 20                      | Y          | H,K,K,S            |                 | MRI,Xr,Scint  | 96              | 60              | 10-60 | 20       | 2016            | Y   | ?                                                                      |         |
|        | 2    | 29  | M      | Ch  | >12          | >15                     | Y          | H,H,S,S            |                 | MRI,Xr        | 80              |                 | 10-80 |          |                 | Y   | ?                                                                      |         |
| 20     | 1    | 25  | F      | Ch  | 120          | 156                     | Y          | H,H,S              |                 | Xr,MRI,Scinti | 60              | Y?              | ?     | ?        | ?               | Y   | ?                                                                      |         |
|        |      |     |        |     |              |                         |            |                    |                 |               |                 |                 |       |          |                 |     | Granulomatous bone lesions. Multiple CS over10 years                   |         |

Table 1. — Continuation

| Ref | Case               | Age | Gender | IBD | ON         |                         |            |             |                 |    | Corticosteroids |         |           |                 |     | BMD | Remarks                                                                                                                      |
|-----|--------------------|-----|--------|-----|------------|-------------------------|------------|-------------|-----------------|----|-----------------|---------|-----------|-----------------|-----|-----|------------------------------------------------------------------------------------------------------------------------------|
|     |                    |     |        |     | Pain onset | Delay after start of CS | Multifocal | Sites of ON | Diagnostic tool | IV | Mean daily dose | Range   | Duration  | Cumulative dose | TPN |     |                                                                                                                              |
| 21  | 1                  | 14  | F      | Ch  |            | No CS                   | ?          | both ankles | Xr, Scinti      | No | No              | No      | No        | No              | No  | ?   | Bad figure to show ON. Pain in left knee, hips, hands. Radiological "penia" at hips and knee but no ON. Xr wrists and St; N. |
| 22  | 1                  | 50  | F      | UC  | 144        | 144                     | Y          | H,H,S       | Xr,MRI          | ?  | 38              | ?-60    | 3         | 3.7             | ?   | ?   |                                                                                                                              |
| 22  | 2                  | 39  | F      | Ch  | 122        | 122                     | Y          | H,H,K,K     | Xr,MRI          | ?  | Y? (high-dose)  |         | > 3       | ?               | Y   | ?   | Hips Scinti - with MRI +                                                                                                     |
| 22  | Series of 23 cases |     |        |     |            |                         |            |             | Xr              |    | 20.6            | 12-35.5 | 25 (3-80) | 15.4            |     |     | MRI perhaps in some cases                                                                                                    |
| 22  | 1                  |     | F      | UC  | ?          | 36                      | Y          | H,H,K,K,S,S |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 2                  |     | M      | UC  | ?          | 420                     | Y          | H,H,K       |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 3                  |     | M      | UC  | ?          | 108                     | N          | H,H         |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 4                  |     | F      | UC  | ?          | 108                     | N          | H           |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 5                  |     | M      | Ch  | ?          | ?                       | N          | K,K         |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 6                  |     | F      | Ch  | ?          | 192                     | Y          | H,H,K       |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 7                  |     | F      | Ch  | ?          | 504                     | Y          | H,H,S,S     |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 8                  |     | F      | UC  | ?          | 252                     | Y          | H,H,S       |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 9                  |     | M      | Ch  | ?          | 408                     | N          | H,H         |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 10                 |     | F      | Ch  | ?          | 372                     | N          | H,H         |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 11                 |     | M      | Ch  | ?          | ?                       | Y          | H,H,S,S     |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 12                 |     | M      | Ch  | ?          | ?                       | N          | K,K         |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 13                 |     | F      | Ch  | ?          | ?                       | N          | H,K         |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 14                 |     | M      | Ch  | ?          | 240                     | N          | H           |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 15                 |     | M      | UC  | ?          | 36                      | N          | H,H         |                 | ?  | Y?              | ?       | ?         | ??              | ?   | ?   |                                                                                                                              |
| 22  | 16                 |     | M      | Ch  | ?          | 96                      | Y          | H,H,K       |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 17                 |     | F      | Ch  | ?          | 228                     | N          | H           |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 18                 |     | F      | Ch  | ?          | 132                     | Y          | H,H,K,K     |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 19                 |     | M      | Ch  | ?          | ?                       | N          | H           |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 20                 |     | M      | UC  | ?          | ?                       | N          | H,H         |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |
| 22  | 21                 |     | F      | UC  | ?          | ?                       | N          | H,H         |                 | ?  | Y?              | ?       | ?         | ?               | ?   | ?   |                                                                                                                              |

|    |        |    |         |           |                          |                                        |            |                                                                    |            |                             |                    |                              |                               |           |            |    |                             |
|----|--------|----|---------|-----------|--------------------------|----------------------------------------|------------|--------------------------------------------------------------------|------------|-----------------------------|--------------------|------------------------------|-------------------------------|-----------|------------|----|-----------------------------|
| 22 | 22     |    | F       | Ch        | ?                        | ?                                      | N          | H,H                                                                |            | ?                           | Y?                 | ?                            | ?                             | ?         | ?          | ?  |                             |
| 22 | 23     |    | F       | UC        | ?                        | 36                                     | Y          | H,H,K,K                                                            |            | ?                           | Y?                 | ?                            | ?                             | ?         | ?          | ?  |                             |
| 23 | 1      | 25 | F       | UC        | ?                        | ?                                      | Y          | H,H,K,K                                                            | Xr         | Y?                          | Y?                 | ?                            | 7                             | ?         | ?          | P  |                             |
| 24 | 1      | 56 | M       | UC        | ?                        | ?                                      | ?          | H?                                                                 | MRI        | No                          | Y                  | ?-80                         | 48                            | 19.9      | ?          | N  | Hips MRI prospectively done |
| 24 | 2      | 44 | M       | UC        | ?                        | ?                                      | ?          | H?                                                                 | MRI        | Y?                          | Y?                 | ?-80                         | 120                           | 18.1      | ?          | N  | Hips MRI prospectively done |
| 24 | 3      | 37 | M       | UC        | ?                        | ?                                      | ?          | H?                                                                 | MRI        | No                          | Y?                 | ?-50                         | 48                            | 18.7      | ?          | N  | Hips MRI prospectively done |
| 24 | 4      | 25 | M       | UC        | ?                        | ?                                      | ?          | H?                                                                 | MRI        | Y                           | Y?                 | ?-80                         | 24                            | 5.6       | ?          | ND | Hips MRI prospectively done |
| 24 | 5      | 40 | M       | UC        | ?                        | ?                                      | ?          | H?                                                                 | MRI        | No                          | Y?                 | ?-80                         | 1.1                           | 3.5       | ?          | ND | Hips MRI prospectively done |
|    | n = 51 | 31 | M28/F23 | Ch29/UC21 | n = 19 : 31.72 (0d-144m) | n = 32 : 117.0 (2d-504d) Median 10.35m | Y24/N20/?7 | H12/HH28/K5/KK15/S5/SS5/E1b1/Both E1b1/talus2/both talus 1/lunate1 | MRI15/X-24 | CS : Y50/51 IV : Y15/N8/?28 | n = 14 + 23 : 8-80 | n = 22 + 23 : 1.1-120(18, 8) | n = 15 + 23 : 9.75 (1.8-19.9) | Y8/N7/?36 | N3/P4 /Op2 |    |                             |

Table 2. — **Doubtful ON cases**

Ref = reference of the article. Gender : M = male, F = female. IBD : Ch = Crohn's disease, UC = ulcerative colitis. CS = corticosteroids. Pain onset and delay in months.  
Multifocal = more than two sites. Sites of ON : H = hip, K = knee, S = shoulder. Diagnostic tool : Xr = radiography, Scinti = scintigraphy. Mean daily and range in mg prednisone.  
Cumulative dose = in g prednisone. TPN = total parenteral nutrition. BMD = bone mineral density (by DEXA). SI = sacroiliac joint.

| Ref | Case | Age | Gender | IBD | ON         |                         |            |             |                 |      | Corticosteroids |                 |       |                  |                 |     | TPN | BMD                                                                                                                     | Remarks                                                           |
|-----|------|-----|--------|-----|------------|-------------------------|------------|-------------|-----------------|------|-----------------|-----------------|-------|------------------|-----------------|-----|-----|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
|     |      |     |        |     | Pain onset | Delay after start of CS | Multifocal | Sites of ON | Diagnostic tool | IV   |                 | Orally          |       |                  |                 |     |     |                                                                                                                         |                                                                   |
|     |      |     |        |     |            |                         |            |             |                 | Dose | Duration (day)  | Mean daily dose | Range | Duration (month) | Cumulative dose |     |     |                                                                                                                         |                                                                   |
| 12  | 5    | 22  | M      | Ch  | > 1        | > 2                     | N          | H,H         | Scinti          | ?    | ?               | 12              | ?     | ?                | 4,7             | 1.8 | ?   | No confirmation by Xr, biopsy or MRI                                                                                    |                                                                   |
| 12  | 6    | 27  | M      | UC  | 23         | ?                       | N          | K           | Scinti          | Y?   | 30              | ?               | ?     | ?-60             | 7               | ?   | Y   | No confirmation by Xr, biopsy or MRI                                                                                    |                                                                   |
| 12  | 7    | 36  | M      | UC  | > 3        | > 5                     | N          | K,K         | Scinti          |      | ?               | 20              | ?     | ?                | 18,7            | 12  | ?   | No confirmation by Xr, biopsy or MRI                                                                                    |                                                                   |
| 16  | 1    | 17  | F      | Ch  | 6          | 6                       | N          | H,H         | Xr,CT,MRI       | ?    | ?               | Y?              | ?     | ?                | ?               | ?   | ?   | Xr ON st 3? MRI = diffuse edema. Reconstruction S13 to St 2 after decompression? Confusion with Transient Osteoporosis? |                                                                   |
| 17  | 1    | 19  | M      | Ch  | >36        | >36                     | N          | K,K         | Xr              | No   | No              | Y = ACTHx2/w    |       |                  | 12              | ?   | N   | ?                                                                                                                       | Possible confusion with dissecans osteochondritis (loose bodies!) |
| 19  | 3    | 36  | M      | Ch  |            |                         | N          | H, H        | Xr              | No   | No              | No              | No    | No               | No              | No  | N   | ?                                                                                                                       | SPA+                                                              |
| 19  | 4    | 10  | M      |     |            |                         | N          | H,H         |                 | No   | No              | No              | No    | No               | No              | No  | N   | ?                                                                                                                       | SPA suspected (SI+)                                               |
| 21  | 1    | 14  | F      | Ch  | ?          | ?                       | N          | Both talus  | Xr,Scinti       | No   | No              | No              | No    | No               | No              | No  | N   | ?                                                                                                                       | Bad illustration of radiological lesions. SPA possible (SI N)     |

tory IBD with long-term CS therapy.” Unfortunately, the paper did not include a description of the inclusion criteria used for this series. The other reviews were retrospective studies and presented other problems. No details regarding the diagnostic procedures or methodology used were found for the first review (9). Moreover, we found some doubtful diagnoses in both reviews (Table 2). Given that the number of published cases is very low in comparison with the estimated prevalence of ulcerative colitis (70-150/100,000) and Crohn’s disease (20-40/100,000) (22), an incidence rate of 0.17% to 2.6% seems too high. This could be because of ON misdiagnoses ; however, before any conclusions are drawn, more data is required. A prospective study should be conducted specifically to detect ON.

We reviewed the proposed etiological factors. Given that only one ON case was unassociated with CS, a closer relationship between ON and CS than between ON and IBD seems likely. However, as the reported data are generally incomplete, we can only highlight trends. The mean delay between CS therapy initiation and ON diagnosis we found is probably atypical. A delay of 1 month or less, which we reported in three cases, is unusual. Such a short delay suggests that ON had been present prior to CS therapy. These three had undergone previous CS therapies which could be linked to ON onset. However, the absence of a systematic ON screening in IBD patients receiving corticosteroids limits the conclusions that can be drawn. Our review does not support the assertion that ON may develop in IBD patients who are not receiving CS therapy. As only one such case has been reported, we believe there is a link between ON and IBD treated with CS, but not between ON and IBD. High doses of CS, including steroid pulse therapy, were frequently observed when CS therapy details were available. The possible deleterious effect of such CS therapy has been suggested due to its association with the ON development in lupus patients (29). Interestingly, the duration and the cumulative dose of CS therapy for ON patients with IBD appear to be lower than for ON patients with other diseases like lupus (31). In our review, the mean duration was 18.8 months, as compared to 58 months in the lupus with ON series from Zizic *et al.*, while the cumulative prednisone dose was 9.75 g, compared to 42 g in the lupus series (31). This implies that a predisposing factor might exist in some IBD patients treated with CS that does not exist in lupus patients.

Authors have discussed other physiopathological factors for ON, such as lipid embolism due to lipid emulsions (8,16), osteoporosis (21), or coagulation factor disorders (8,18,19,21). Our review draws no conclusions on these points. Some authors have also suggested a relationship between ON and total parenteral nutrition (TPN) (8,16), as acute IBD patients are sometimes treated with total parenteral nutrition (lipid emulsions). However, every case that employed total parenteral nutrition also used high doses of corticosteroids ; therefore, it is impos-

sible to draw conclusions on the possible role of total parenteral nutrition in ON development. Osteoporosis, a complication of CS therapy, was also suspected to be an etiological factor for ON (25,26). The available data are too incomplete for any conclusion to be drawn. Though osteoporosis may play a role, it does not appear to be a major etiological factor in ON development.

Microvascular occlusion resulting from hypercoagulability and defective fibrinolysis have been proposed as another causative mechanism for ON development (27), as venous and arterial thromboses increase in IBD patients (28,29). Once again, no definitive conclusion is possible.

## In summary

ON could be a complication of IBD, especially when IBD is treated with CS therapy. In this review, including three of our own cases in addition to other published cases, two distinctive features were found to distinguish CS therapy for IBD patients with ON and CS therapy for patients with other diseases and ON. First, ON may occur after a lower cumulative dose and a shorter CS therapy duration in IBD patients. Second, ON is multifocal in most IBD patients.

For clinical practice, we suggest regular ON checkups using MRI for patients suffering from IBD and treated with CS therapy.

## Research agenda for the future

Further studies investigating the relationship between IBD, ON, and corticosteroids and exploring possible individual susceptibilities are warranted.

## References

1. MARCUS N.D., ENNEKING W.F., MASSAM R.A. The silent hip in idiopathic aseptic necrosis. Treatment by bone-grafting. *J. Bone Joint Surg. Am.*, 1973, **55** : 1351-66.
2. RESNIK D., NIWAYAMA G. Osteonecrosis : Diagnostic techniques, specific situations, and complications. In : Resnik D, ed. *Diagnosis of Bone and Joint Disorders*. 3<sup>rd</sup> ed. Philadelphia : Saunders Company, 1995 : 3495-557.
3. HAUZEUR J.P., PASTEELS J.L. Bone biopsy as diagnostic criteria for aseptic necrosis of the femoral head. In : Schoutens A, Arlet J, Gardeniers JWM, Hugues SPF, eds *Bone circulation and vascularization in normal and pathological conditions*. New York : Plenum Press, 1993 : 277-81.
4. HAUZEUR J.P., PASTEELS J.L., SCHOUTENS A., HINSENKAMP M., APPELBOOM T., CHOCHRAD I., PERLMUTTER N. The diagnostic value of magnetic resonance imaging in non-traumatic osteonecrosis of the femoral head. *J. Bone Joint Surg. Am.*, 1989, **71** : 641-9.
5. MITCHELL D.G., RAO V.M., DALINKA M.K., SPRITZER C.E., ALAVI A., STEINBERG M.E., FALLON M., KRESSEL H.Y. Femoral head avascular necrosis : correlation of MR imaging, radiographic staging, radionuclide imaging, and clinical findings. *Radiology*, 1987, **162** : 709-15.
6. HAUZEUR J.P., SINTZOFF S. JR., APPELBOOM T., DE MAERTELAER V., BENTIN J., PASTEELS J.L. Relationship between magnetic resonance imaging and histologic findings by bone biopsy in non-traumatic osteonecrosis of the femoral head. *J. Rheumatol.*, 1992, **19** : 385-92.
7. BROM B., BANK S., MARKS I.N., COBB J.J. Periostitis, aseptic necrosis and arthritis in a patient with Crohn’s disease. *Gastroenterology*, 1971, **60** : 1106-9.

8. SHAPIRO S.C., ROTHSTEIN F.C., NEWMAN A.J., FLETCHER B., HALPIN T.C. Jr. Multifocal osteonecrosis in adolescents with Crohn's disease : a complication of therapy ? *J. Pediatr. Gastroenterol. Nutr.*, 1985, **4** : 502-6.
9. VAKIL N., SPARBERG M. Steroid-related osteonecrosis in inflammatory bowel disease. *Gastroenterology* 1989 ;96 :62-7.
10. CULP R.W., SCHAFFER J.L., OSTERMAN A.L., BORA F.W. JR. Kienböck's disease in a patient with Crohn's enteritis treated with corticosteroids. *J. Hand. Surg. (Am.)*, 1989, **14** : 294-6.
11. RUTTENBERG D., BURNS D., LEARMONTH I., HESELSON N. Steroid-related avascular necrosis and Crohn's disease. *S. Afr. Med. J.*, 1990, **77** : 426.
12. MADSEN P.V., ANDERSEN G. Multifocal osteonecrosis related to steroid treatment in a patient with ulcerative colitis. *Gut*, 1994, **35** : 132-4.
13. MALCORPS J., EEKHAUT M., DIERCKXSENS P. Bilateral stage III osteonecrosis of the femoral head treated with core decompression. Case report and review of the literature. *Acta Orthop. Belg.*, 1996, **62** : 241-3.
14. ARNOLD C.A., TAVARES J.O. Long-term follow-up of bilateral steroid-induced osteonecrosis of the lateral femoral condyles in a patient with Crohn's disease. *Am. J. Knee Surg.*, 1998, **11** : 236-40.
15. REIMUND J.M., SIBILIA J., DURCKEL J., BRUNET B., LOTH F., KUNTZ J.L., DUCLOS B., BAUMANN R. Epiphysis-metaphysis bone ischemia in hemorrhagic rectocolitis and Crohn's disease. *Gastroenterol. Clin. Biol.*, 1998, **22** : 634-8.
16. FREEMAN H.J., FREEMAN K.J. Prevalence rates and an evaluation of reported risk factors for osteonecrosis (avascular necrosis) in Crohn's disease. *Can. J. Gastroenterol.*, 2000, **14** : 138-43.
17. FREEMAN H.J., KWAN W.C. Brief report : non-corticosteroid-associated osteonecrosis of the femoral heads in two patients with inflammatory bowel disease. *N. Engl. J. Med.*, 1993, **329** : 1314-6.
18. KHAN A., ILLIFE G., HOUSTON D.S., BERNSTEIN C.N. Osteonecrosis in a patient with Crohn's disease unrelated to corticosteroid use. *Can. J. Gastroenterol.*, 2001, **15** : 765-8.
19. KLINGENSTEIN G., LEVY R.N., KORNBLUTH A., SHAH A.K., PRESENT D.H. Inflammatory bowel disease related osteonecrosis : report of a large series with a review of the literature. *Aliment Pharmacol. Ther.*, 2005, **21** : 243-9.
20. VIDAL CASARIEGO A., DE LA CUERDA COMPÉS C., BRETÓN LESMES I., CAMBLOR ALVAREZ M., VELASCO GIMENO C., GARCÍA PERIS P. Avascular necrosis of both hips and knees in a patient with ulcerative colitis treated for a long term with high-dose corticosteroids. *Nutr. Hosp.*, 2006, **21** : 109-12.
21. KAMATA N., OSHITANI N., SOGAWA M., YAMAGAMI H., WATANABE K., FUJIWARA Y., ARAKAWA T. Usefulness of magnetic resonance imaging for detection of asymptomatic osteonecrosis of the femoral head in patients with inflammatory bowel disease on long-term corticosteroid treatment. *Scand. J. Gastroenterol.*, 2007, **5** : 1-6.
22. GLICKMAN R.M. Inflammatory bowel disease. In : PETERSDORF R.G., ADAMS R.D., BRAUWALD E., ISSELBACHER K.J., MARTIN J.B., WILSON J.D. (eds). *Harrison's principles of internal medicine*, 14<sup>th</sup> ed London : Mac Graw-hill international book company ; 1998 : 1633-45.
23. LAPORTE D.M., MONT M.A., MOHAN V., JONES L.C., HUNGERFORD D.S. Multifocal osteonecrosis. *J. Rheumatol.*, 1998, **25** : 1968-74.
24. COLLABORATIVE OSTEONECROSIS GROUP. Symptomatic multifocal osteonecrosis. A multicenter study. *Clin. Orthop. Relat. Res.*, 1999, **369** : 312-26.
25. LAURENT J., MEUNIER P., COURPRON P., EDOUARD C., BERNARD J., VIGNON G. Research on the pathogenesis of aseptic necrosis of the femoral head. Evaluation of the constitutional bony factors in 35 cases of iliac crest biopsy. *Nouv. Presse Med.*, 1973, **2** : 1755-60.
26. WEINSTEIN R.S., JILKA R.L., PARFITT A.M., MANOLAGAS S.C. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J. Clin. Invest.*, 1998, **102** : 274-82.
27. GLUECK C.J., FREIBERG R.A., FONTAINE R.N., TRACY T., WANG P. Hypofibrinolysis, thrombophilia, osteonecrosis. *Clin. Orthop. Relat. Res.*, 2001, **386** : 19-33.
28. BERNSTEIN C.N., BLANCHARD J.F., HOUSTON D.S., WAJDA A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease : a population-based cohort study. *Thromb. Haemost.*, 2001, **85** : 430-4.
29. BERNSTEIN C.N., WAJDA A., BLANCHARD J.F. The incidence of arterial thromboembolic diseases in inflammatory bowel disease : a population-based study. *Clin. Gastroenterol. Hepatol.*, 2008, **6** : 41-5.
30. NAGASAWA K., TADA Y., KOARADA S., HORIUCHI T., MURAI K., UEDA A., YOSHIZAWA S., OHTA A. Very early development of steroid-associated osteonecrosis of the femoral head in systemic lupus erythematosus : prospective study by MRI. *Lupus*, 2005, **14** : 385-90.
31. ZIZIC T.M., MARCOUX C., HUNGERFORD D.S., DANSEREAU J.V., STEVENS M.B. Corticosteroid therapy associated with ischemic necrosis of bone in systemic lupus erythematosus. *Am. J. Med.*, 1985, **79** : 596-604.