Clinical characteristics of pediatric patients with acne fulminans associated to chronic non-bacterial osteomyelitis

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List of Abbreviations: AF (Acne Fulminans), CNO (Chronic Non-bacterial Osteomyelitis), CRMO (Chronic Recurrent Multifocal Osteomyelitis), NSAID Nonsteroidal Anti-Inflammatory Drugs, SSZ Sulfasalazine, CRP C-Reactive Protein, ESR Erythrocyte Sedimentation Rate

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ABSTRACT

Objective

Acne fulminans (AF) is a rare, explosive systemic form of acne. Chronic non-bacterial osteomyelitis (CNO) or chronic recurrent multifocal osteomyelitis (CRMO) is a primarily pediatric autoinflammatory disorder characterized by sterile osteolytic bone lesions. Concomitant occurrence of CNO/CRMO and AF is very rare and little is known about the epidemiological and clinical particularities of this association. The aim of this retrospective observational study was to describe the characteristics of pediatric patients with CNO/CRMO associated to AF.

Methods

Electronic mailing lists of French medical societies were used to call for patients with CNO/CRMO and AF. A search for published patients with CNO/CRMO and AF was performed by screening PubMed.

Results

We identified 5 original patients and 10 patients from the literature. All patients were adolescent boys. Mean age at disease onset was 14.9 years. 9/15 patients had received isotretinoin before the sudden onset of AF. Osteoarticular symptoms appeared within less than 1-3 months after the onset of AF. The mean numbers of clinical and radiological bone lesions were 3.6 and 5.6. The percentages of patients with involvement of vertebrae, pelvis, chest and cranial were 40%, 40%, 30%, 6.6%. Arthritis was observed in 69.2% of patients and sacroiliac arthritis in 46.2%.

Conclusion

CNO/CRMO associated to AF occurs predominantly in male adolescents and is characterized by frequent involvement of the axial skeleton and arthritis. Epidemiological and clinical features of these patients differ from general CNO/CRMO cohorts. Clinical management requires careful handling of isotretinoin doses.

Key terms: Acne fulminans, Chronic non-bacterial osteomyelitis, chronic recurrent multifocal osteomyelitis, Isotretinoin

Introduction

Acne fulminans (AF) is a rare systemic disease that predominantly affects adolescent boys. Most patients previously have mild to moderate acne before the sudden onset of hemorrhagic ulcerative papules and nodules associated with a wide spectrum of systemic reactions (fatigue, malaise, arthralgias, myalgias, fever) and abnormal laboratory findings (anaemia, leucocytosis, elevated CRP and ESR).[1,2] It is extremely painful and results in extensive scarring. A recent review estimated that less than 200 cases are known. AF should not be confused with acne conglobata or severe acne vulgaris (for comparison see supplementary data 1).

Chronic non-bacterial osteomyelitis (CNO) is an idiopathic, non-infectious inflammatory bone disorder. It covers a wide clinical spectrum with unifocal and timely limited courses at one end, and prolonged multifocal, recurrent, sometimes destructive disease courses at the other end, which is usually referred to as chronic recurrent multifocal osteomyelitis (CRMO)[3]. CNO/CRMO is primarily a pediatric disorder but can persist into adulthood or have an adult-onset[4]. Its incidence has been estimated at 0.4/100.000/year[5]. Osteomyelitis is typically localized in metaphyses and epiphyses of long bones[4,6]. CNO/CRMO can be associated with inflammatory conditions of joints, the intestine and the skin[1–3].

Concomitant occurrence of CNO/CRMO and AF is extremely rare and little is known about the clinical particularities of these patients. Therefore, we conducted a retrospective observational study to describe the epidemiological and clinical characteristics of pediatric patients with CNO/CRMO associated to AF.

Methods

Patients were identified through calls to the French Society of Pediatric Inflammatory Diseases and the French Society of Pediatric Dermatology. Inclusion criteria were: i) at least one episode of AF as defined by published criteria[2], ii) diagnosis of CNO/CRMO by the physician in charge

of the patient, with presence of at least one lesion (documented by MRI or skeletal scintigraphy, in favour of the diagnosis of osteomyelitis, iii) absence of detectable infection, iv) onset before 18 years of age.

We retrospectively collected the following data: Age at onset of AF and CNO/CRMO, diagnostic delay, sex, personal and familial medical history, treatments, systemic signs, results from blood tests, description and localisation of skin lesions, number of clinical and radiological bones lesions, presence of arthritis, treatment and evolution. Osteolytic lesions and/or arthritis localized in vertebrae, sacrum, iliac bones or rip cage were designated "axial involvement". All patients were informed about the study and gave consent. The study was approved by French regulatory authorities (CNIL n°2212602).

A search for published patients with AF and CNO/CRMO was performed by screening PubMed using the following research terms alone and their combinations: ″chronic recurrent multifocal osteomyelitis", *"acne fulminans", "fulminant acne", "CNO", "chronic non-bacterial osteomyelitis", "CRMO"* and "*SAPHO"*. We only considered articles with data allowing confirmation of the inclusions criteria (same as above).

Results

Five patients were included in the study. All of them were male. Patient 1 had a positive family history of severe, non-fulminant acne. Patient 3 had a family history of psoriasis. None had a personal medical history of pustulosis or IBD. Antinuclear antibodies were negative in all patients. HLA-B27 was negative in 4 patients and data was missing in for patient 3.

The ages at onset of AF were respectively 14.1, 16.4, 13.3, 15.1 and 14.3 years. In all patients, cutaneous lesions were localised on thorax, back and the face. Patient 5 also had lesions on upper extremities. Some examples of cutaneous manifestations are shown in Figure 1a-c. All patients had mild or moderate acne for months or years before sudden exacerbation

occurred. Two weeks before the onset of AF patient 1 and 3 were treated with oral isotretinoin at a dose of 0,3mg/kg/day and 0,6 mg/kg/day. Drugs administrated after exacerbation of AF are shown in table 1. All patients had a scarring evolution of skin lesions (Fig.1c).

All Patients showed elevated CRP levels (mean 82mg/dl (range 20 to 134; Table 1). ESR was elevated in 4 patients (mean 54mm/1h (range 40 to 70)) and was not available in one patient. Systemic symptoms (fever, asthenia or emaciation) were observed in patients 1, 2 and 3.

Osteoarticular manifestations appeared within 1-3 months after onset of AF in all patients (Table 1). The delay from onset of osteoarticular manifestations to diagnosis of CNO/CRMO was $\leq$ 1 month in all patients. The mean number of bone lesions with clinical manifestations was 3.6 (range 3-4) and the mean number of lesions detected on body MRI was 5.6 (range 4-9). The localizations of clinical and radiological bone lesions are shown in table 1. Axial involvement was observed in patients 2, 3, 4 and 5 (Table 1). Arthritis was observed in all patients and affected the knee in patients 1 and 5, the sacroiliac joints in patients 2, 3, 4 and 5, and the ankles in patient 5 (Table 1). Treatments used for bone lesions are summarized in table 1. At the last follow up visit 12-30 months after the diagnosis, osteoarticular remission of CNO/CRMO was achieved for all patients. Patients 1, 2 and 3 had complete remission of acne, whereas patients 4 and 5 had persistent non-severe acne. All patients had cutaneous scars.

Using the same inclusions criteria our literature research identified 7 articles reporting on 10 pediatric CNO/CRMO patients with AF[7–13]. Epidemiological and clinical data from these patients are summarized in table 1. Several other reports did not provide sufficient data on skin lesions to establish the diagnosis of AF. All patients were male adolescents aged from 13-17 years (Table 1). Three patients received isotretinoin before the onset of AF at doses of 0,5-1mg/kg/day. 8/10 patients had axial involvement. Arthritis occurred in 4/8 patients with

available data (Table 1). The localizations of bone lesions and arthritis, clinical data, treatments and available biological data of these patients are shown in table 1.

In order to further compare clinical characteristics of the study cohort and general CNO/CRMO populations, we arbitrarily chose to compare patients' profiles to the two largest published CNO/CRMO cohorts (Table 2) : the national French cohort (n=178 patients) and the international Eurofever registry cohort (n=486 patients)[4,6]. In our study cohort, the mean number of bone lesions detected by MRI was 4.2, resembling findings from the French and Eurofever cohorts (mean 3.5 and 4.1)[4,6]. However, the percentage of patients with involvement of vertebrae (40%), pelvis (40%) or chest (33.3%) was increased (Table 2). Furthermore, we observed a high prevalence of arthritis (69.2%), when compared to the French and the Eurofever cohorts (11% and 32%; Table 2).

Discussion

Our observations suggest that the epidemiological and clinical features of patients with CNO/CRMO associated to acne fulminans differ from general CNO/CRMO cohorts. The association of AF and CNO/CRMO was exclusively observed in male adolescents. In contrast, a female predominance has been reported in general CNO/CRMO cohorts[4,6].

CNO/CRMO associated to AF is characterized by frequent involvement of the axial skeleton and arthritis. Our observations in pediatric patients with OCN/OCMR and AF are similar to SAPHO patients where development of peripheral arthritis can be observed in 23-44% of the patients, and axial arthritis in up to 91.9% of the adult patients[14,15]. Whether, CNO/CRMO associated to AF may be considered as a subtype of SAPHO syndrome or part of an independent auto-inflammatory disease remains to be determined.

Bone lesions appeared within less than 1-3 months after onset of AF in 10/11 patients. Synchronous exacerbation of severe acne and bone lesions has also been observed in the literature[16]. Furthermore, Cutibacterium (formerly Propionibacterium) acnes has been proposed to play a role in the pathogenesis of CNO/CRMO and other autoinflammatory diseases[17]. Our observations further support the idea of a possible link between onset of acne and development of CNO/CRMO.

It is to note 9/15 patients were treated with isotretinoin shortly before onset of AF and CNO/CRMO in order to treat severe, non-fulminant acne. Isotretinoin is known to increase metabolic burst from peripheral blood neutrophils and expression of genes relating to innate immune activation[18,19]. An ambiguous role of isotretinoin for the treatment of severe acne has been reported previously[1,2,18,20]. Treatment with isotretinoin needs to be initiated at low doses 0.1 mg/kg/day and only then doses are increased progressively[1,2]. When initiated directly at high doses, isotretinoin can exacerbate acne and induce AF[1,2]. In our study cohort isotretinoin treatment was initiated at relatively high doses (0.3-1 mg/kg/day). Thus, one could hypothesise

that the extent of inflammation induced by isotretinoin and/or AF may contribute to triggering CNO/CRMO. Further studies are required to confirm (or infirm) the role of isotretinoin and/or AF for the development of CNO/CRMO and to determine whether this clinical presentation corresponds to a particular monogenetic autoinflammatory disease[21,22].

The recommended treatment for AF with systemic symptoms is a combination of corticosteroids and isotretinoin[2]. Oral corticosteroids should be started first, at high doses (0.5-1.0 mg/kg/day) for ≥4 weeks until lesions heal. Isotretinoin is then started at the initial dose of 0.1 mg/kg/day in association with corticosteroids for 4 weeks. If no flare is observed, the same dose of isotretinoin is maintained for at least 4 more weeks, and corticosteroid doses are gradually tapered. Isotretinoin doses are then progressed increased gradually over 3-5 months as tolerated. The typical isotretinoin cumulative dose is 120-150 mg/kg. Only 1/3 of patients presented in this study were treated accordingly. Management of AF associated to CNO/CMRO requires a close collaboration of dermatologists and rheumatologists.

Our study has some methodological limitations. Identification of patients via mailing lists to medical societies may have caused selection bias. Furthermore, the retrospective design of our study may have introduced information bias, especially because of the mode of data collection (questionnaire).

In conclusion, CNO/CRMO associated to AF occurs predominantly in male adolescents and is characterized by frequent involvement of the axial skeleton and arthritis. Epidemiological and clinical features of these patients differ from general CNO/CRMO cohorts. Clinical management requires careful handling of isotretinoin doses.

List of Abbreviations: AF (Acne Fulminans), CNO (Chronic Non-bacterial Osteomyelitis), CRMO (Chronic Recurrent Multifocal Osteomyelitis), NSAID Nonsteroidal Anti-Inflammatory Drugs, SSZ Sulfasalazine, CRP C-Reactive Protein, ESR Erythrocyte Sedimentation Rate

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Figure legends

Figure 1. Illustration of skin lesions. Active ulcerated, haemorrhagic, and covered with crusts skin lesions (A, B) and scarring evolution (C).

Table 1. Epidemiological and clinical characteristics of patients reported in this study and in the literature. # time between onset of osteoarticular symptoms and diagnosis of CNO/CRMO. Ctc-Corticosteroids; MTX-Methotrexate.

Table 2: CNO/CRMO with acne fulminans compared to selected general CNO/CRMO cohorts. Calculations were performed based on patients with available data concerning the explored item. *data missing for 2 patients. #data missing for 5 patients. "data missing for 1 patient.

Supplementary data 1. Distinguishing features in acne fulminans, acne conglobata and acne vulgaris

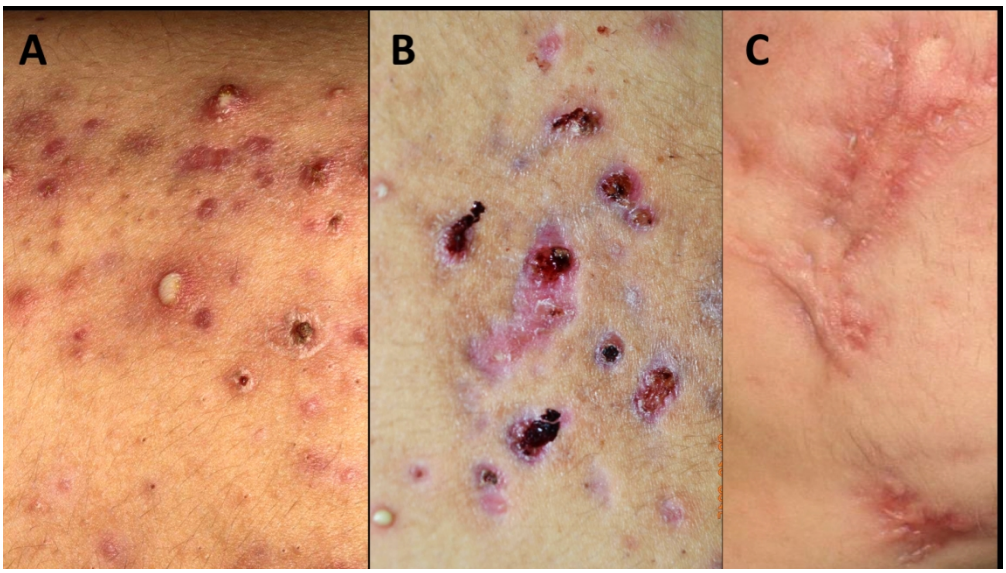

Figure 1. Illustration of skin lesions. Active ulcerated, haemorrhagic, and covered with crusts skin lesions (A, B) and scarring evolution (C).

474x266mm (86 x 86 DPI)

	Sex	Age at onset of AF (years)	Delay Onset Acne to onset bone pain (months)	Diagnostic delay # (months)	Initial localization - Clinical	Initial localization - Imagery	Arthritis	Isotretinoin before onset bone symptoms	Systemic Signs	CRP mg/dl	Treatment for osteo-articular involvement	Treatment for acne	Bone lesions Remission	Acne Remission	Follow up
Patients reported in this study															
Patient 1	M	14.1	3	1	Hip R Ankle L	Humerus x2, Distal & proximal femoral metaphyses, Tibia x2, Heel R	Knee R	Yes	Yes	68	NSAID	Ctc Isotretinoin	Yes	Yes Scars	30
Patient 2	M	16.4	3	<1	Shoulders x2, Knees x2, Lumbar and sacral spine, Sacroiliitis x2	Femur x2, Fibula L, Humerus R, Pelvis R, Sacrum L, T8/T9, L2/L3	Sacroiliitis x2	No	Yes	108	NSAID	Ctc, Isotretinoin, Clindamycin (1month)	Yes	Yes Scars	14
Patient 3	M	15.3	1,5	<1	Sacroiliitis G, Sacrum, Sternum	Sternum, Coccyx, S4, Sacroiliitis L	Sacroiliitis L	Yes	Yes	134	NSAID	Isotretinoïn, Ciprofloxacin (some days)	Yes	Yes Scars	20
Patient 4	M	15.1	1	<1	Low dorsal spine and high lumbar spine, Sacroiliitis x2	Low dorsal spine high lumbar spine Sacroillitisx2	Sacroiliitis x2	No	No	80	NSAID, Etanercept, MTX, Adalimumab	Erythromycin (topical)	Yes	Yes Scars	14
Patient 5	M	14.3	3	<1	Sternoclavicular L Sacroiliitis R Low dorsal spine	Sternoclavicular L Sacroiliitis R Low dorsal spine	Sacroiliitis R Knees Ankles	No	No	20	NSAID, Ctc ,Etanercept, MTX, Adalimumab	Ketrel diprogena (topical), Cyclin	Yes	Partial Scars	12
Patients reported in the literature															
Pauli et al.[10] Patient 1	M	14y	< 1	3	Clavicle L	Sternum, Clavicula	Sterno-clav L	No	Yes	75	Ctc, Penicilline	Tetracycline	Yes (1 relapse)	Yes (1 relapse)	1 year
Pauli et al.[10] Patient 2	M	15y	<1	NA	Clavicle R	Clavicle R, Wrist R	-	No	Yes	59	Ctc Macrolides	Isotretinoine	Yes (multiple relapses)	Yes (multiple relapses)	7 months
Peleg et al.[14]	M	17y	NA	2	Hipsx2 Clavicles x2	Humerus R, Clavicle L, Sternum, Acromion L	-	Yes 60mg/d	Yes	NA	NSAID, Ctc	Tetracycline	NA	NA	NA
Freira et al.[15]	M	13y	NA	NA	Hip R Sternum	Femur R, Fibula R	Sacroilitis	Yes NA	Yes	2,6	NSAID, MTX	Clindamycine, Isotretinoine	Yes	Partial	NA
Tlougan et al.[9]	M	15y	NA	NA	Ankle R	NA	-	Yes NA	NA	NA	Ctc 3sem	None	Yes	Yes	NA
Chua et al.[11] patient 1	M	13y	NA	144	NA	Skull, Mandibles x2, Jawbone R, Calcaneum x2, Tarsal bones x2	1er MTP R	Yes 1mg/kg/d	NA	NA	Biphosphonate, Methotrexate	NA	Yes	NA	NA
Chua et al.[11] patient 2	M	13y	<1	<1	Dos	Vertebrae	-	Yes 0,5 mg/kg/d	NA	NA	NSAID, Ctc 6weeks, Sulfasalazine	Clindamycine, Isotretinoine	Yes	Yes	NA
Jana et al.[12]	M	16y	1	NA	Spine, Ankle L Clavicle L	NA	Sacroilitis Sterno-clav L	-	Yes	NA	NSAID	Tétracyclines, Oxacilline, Microsurgery	No	Yes	2 years
Erhard et al.[13] Patient 1	M	16y	2	NA	legs x2, Thorax, Kneesx2, Clavicle R	Clavicle R, 3rd Rib L, Knees x2, Tibia R	NA	Yes 40mg/d	No	34	NSAID, CTc, Antibiotics, MTX	Isotretinoine	Yes	NA	3 years
Erhard et al.[13] Patient 2	M	15y	6	<1	Knees x2, Clavicle R	Clavicle, Sternum, T2 1st and 5th Ribs R	NA	Yes 40mg/d	No	52	Antibiotics NSAID	NA	Yes	Yes	18 months

Table 1. Epidemiological and clinical characteristics of patients reported in this study and in the literature. # time between onset of osteoarticular symptoms and diagnosis of CNO/CRMO. Ctc-Corticosteroids; MTX-Methotrexate.

	CRMO associated to severe acne This study	**CRMO French cohort** Wipff et al. [7]	**CRMO Eurofever cohort** Gierschick et al.[6]
Patients, n	15	178	486
Pediatric onset, %	100	100	93.7
Adult onset, %	0	0	6.3
Male, %	100	31	36
Female, %	0	69	64
Age of onset, years, mean	14.9	10.9	9.9
Diagnostic delay, months, mean	<2.1	17	12
Patients with skin lesions, %	100	12	19
Acne %	100	NA	5
Severe acne, %	100	2	NA
Patients with arthritis, %	69.2*	11	32
Monoarthritis, %	30.7*	NA	15
Oligoarthritis, %	30.7*	NA	12
Polyarthritis, %	7.7*	NA	2
Sacroiliac arthritis	46.2*	NA	NA
Patients with IBD; %	0	6	8
Bone lesions, number, mean	4.2*	3.5	4.1
Unifocal, %	21.4	7	29
Multifocal, %	78.6	93	77.8
Clavicle, %	40	10	19
Lower extremity, %	38,5*	47	NA
axial involvement, %	73.3	NA	NA
-Vertebral lesions, %	40	4	23
-Pelvic lesions, %	40	16	25
-Chest lesions, %	33.3	NA	10
-Cranial, %	6.6	2	3
CRP elevated, %	60	51	49
ESR elevated, %	NA	86	59
Treatment			
NSAID, %	73	97	74
SSZ, %	0	12	10
Glucocorticoids, %	60	8	23
Biphosponates, %	0	10	13
TNF blocking agents, %	13.3	7	7
MTX, %	33.3	8	12
Antibiotics, %	76.9*	35	NA
Active osteo-articular disease, after follow up, %	7.1 "	66	50
Follow-up, months, mean	18.7 #	48	NA
Follow-up, months, mean	18.7 #	48	NA

Table 2: CNO/CRMO patients with acne fulminans compared to general CNO/CRMO cohorts. Calculations were performed based on patients with available data concerning the explored item. *data missing for 2 patients. #data missing for 5 patients. "data missing for 1 patient