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Acne fulminans and its multiple associated factors: a systematic review

Background: Acne fulminans (AF) is a severe form of acne that presents with an outburst of haemorrhagic pustules and ulcerations, which may or may not be associated with systemic symptoms and laboratory abnormalities. In the latest classification, four variants of AF are considered, but this does not include AF associated with systemic therapies and inherited genetic syndromes. *Objectives*: To systematically review disease features and evaluate differences among AF. *Materials & Methods*: Related articles were searched using the terms "acne fulminans", "acne conglobata with septicaemia", "acute febrile ulcerative acne" and "pseudo acne fulminans". We searched Medline and Google Scholar from inception to 1977 to identify case reports, case series, commentaries and reviews reporting new AF cases. *Results*: A total of 98 articles met our inclusion criteria. AF induced by higher levels of androgens more frequently presented nodules and cysts than erosions, crusted and haemorrhagic lesions and necrosis. In contrast, patients affected by AF without any apparent cause (referred to here as "miscellaneous AF") more frequently presented with ulcerations and erosions, and patients with AF associated with systemic treatment showed a similar frequency of lesions. Notably, AF in patients with high levels of androgens and AF induced by antibiotics rarely showed comedones. In addition, aseptic osteolytic lesions were more common in miscellaneous AF than other AF. *Conclusion*: AF may present with differences in clinical and laboratory features and associated systemic illnesses, which should be evaluated for the planning of a personalized therapeutic scheme. We propose a classification of AF, according to its association with certain factors.

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Key words: acne fulminans, isotretinoin, review

The term "acne fulminans" (AF) was coined by Plewing and Kligman in 1975. AF is a rare and severe form of inflammatory acne, clinically presenting an abrupt outburst of painful, haemorrhagic pustules and ulceration which may or may not be associated with systemic symptoms, such as fever, polyarthritis and laboratory abnormalities [1].

AF is very rare, accounts for less than 1% of total acne cases [2], and most patients are males, who often present with a history of acne vulgaris over the previous two years [3]. Regarding ethnicity, patients with AF are mostly Caucasians [4].

Traditionally, AF is classified into two different forms, AF and AF without fulminans, depending on whether systemic symptoms are present or not [5]. Recently, the classification has changed to include four variants: AF with systemic symptoms (SS), AF without SS, isotretinoin-associated AF with SS and isotretinoin-associated AF without SS [5]. Although this last classification is more appropriate than the first, cases of AF associated with not only systemic isotretinoin but also other systemic therapies, such as antibiotics, corticosteroids, interferon α2, and inherited genetic syndromes, have been reported.

We conducted a literature review of AF associated with systemic therapies, inherited genetic syndromes and miscellaneous factors in order to determine differences among these subtypes of AF.

Materials and methods

A systematic review of the literature on all published cases of AF was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA statement; prisma-statement.org). The search was conducted through MEDLINE and Google Scholar. Eligibility assessment was performed independently in an unblinded standardized manner by two reviewers. Disagreements between reviewers were resolved by consensus. The flow chart of the search strategy of the review is shown in *figure 1*.

Combinations of the following MeSH terms and key words were used to retrieve all the relevant articles: "acne fulminans", "acne conglobata with septicemia", "acute febrile ulcerative acne" and "pseudo acne fulminans". To identify eligible articles, we screened the titles

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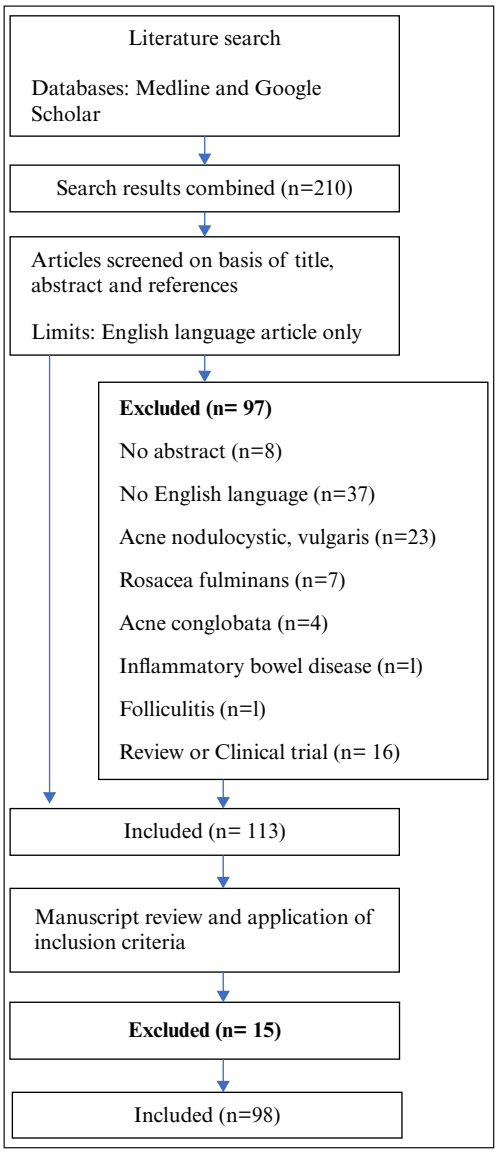

Figure 1. Flow chart of the search strategy for the review.

and abstracts, as well as the full texts. Additionally, the references of the identified articles were manually screened to include relevant articles that might have been overlooked. Full-text reports of the selected articles were included in the analysis.

The inclusion criteria were: articles in English, case reports, case series, commentaries, and reviews reporting new AF cases and focusing on AF. Conversely, all non-English articles, studies reporting a definitive diagnosis other than AF, and literature reviews lacking new case reports were excluded.

The series of information extrapolated from the reviewed articles included: gender, age and ethnicity of patients, history of previous acne, time from previous acne to diagnosis in years, aetiology, cutaneous lesions, site of skin manifestations, symptoms and signs of skin manifestations, laboratory anomalies, cutaneous histology, direct immunofluorescence (DIF), administered therapy, and response to therapy.

Results

A total of 210 articles of AF cases have been reported in the literature since 1977 to date. Articles reported in previous reviews in the literature, which did not satisfy the above-mentioned inclusion criteria, were excluded. Ultimately, 98 articles concerning AF satisfied the above-described inclusion criteria.

Overall, 162 patients [4-100] with AF were described in the selected articles, with a male:female ratio of 14:1 and an average age of 17.35±4.08 years at diagnosis; the minimum and maximum values were 12 years and 40 years, respectively.

Ethnic origin was reported for 28/162 patients [6-28] of whom 15 were Caucasian [4, 8-10, 13-15, 17, 21, 24-26, 28], nine were Asian [11, 12, 16, 18, 22, 23, 27, 29], two were African-(American) [19, 20], and two were Indian/Arab [6, 7].

The course of previous severe acne vulgaris lesions was reported for 129/162 patients [2, 4, 5, 8-11, 13, 15, 17-20, 21-24, 26-81] with a mean and median time from onset of acne vulgaris to AF of 15.79 months and eight months, respectively; the minimum and maximum values for 75 patients were one month and 12 years, respectively.

AF associated with systemic treatment

Forty-eight patients developed AF following systemic therapies, such as isotretinoin, antibiotics, corticosteroids and interferon α2, and these were classified as "AF associated with systemic treatment". Regarding therapies for previous acne, 39 patients developed AF following isotretinoin therapy and six patients following antibiotic therapy, notably lymecycline (2/6 patients) [28, 66], doxycycline (1/6 patients) [22], pristinamycin (1/6 patients) [60] and oxytetracycline (2/6 patients) [65]. Regarding systemic treatment for other diseases, two patients developed AF following corticosteroid therapy [20, 75] and one patient after interferon α2 therapy [94]. AF associated with systemic treatment positively correlated with a history of previous acne vulgaris (47/48).

Isotretinoin-associated AF (*table 1*)

All data on cutaneous lesions, systemic symptoms, and laboratory findings in patients with AFassociated with isotretinoin are summarized in *table 1*. Among 39 patients, ulcerations and erosions, nodules, and crusted and haemorrhagic lesions were the most frequent lesions reported in 66.67%, 53.84% and 46.15% of patients, respectively.

Systemic symptoms were reported in 28 of the 39 patients, especially arthralgia (53.85%) and weight loss (51.28%). Erythema nodosum (EN) and synovitis acne pustulosis hyperostosis osteitis (SAPHO) were the most frequent associated systemic illnesses.

The most frequent laboratory anomalies were: leucocytosis (69.23%), an increase in erythrocyte sedimentation rate (ESR) (58.97%), an increase in C-reactive protein (CRP) (46.15%), and neutrophilia (38.46%).

Administered therapy was reported for 38 of the 39 patients (*table 2*). Overall, the most frequent therapies were systemic corticosteroids (76.31%), systemic

Table 1. Clinical features and laboratory anomalies in patients with AF secondary to systemic treatment (isotretinoin-associated AF, antibiotic-associated AF, corticosteroid and interferon α2-associated AF), high androgen levels, and miscellaneous factors.

	Systemic treatment associated with AF					
	Isotretinoin- associated AF (39/162) [2, 13, 17, 19, 25, 26, 27, 34, 36, 37, 44, 46, 49, 50, 53, 56, 58, 59, 60, 61, 63, 67, 68, 69, 70, 71, 73, 74, 76, 77, 79, 80]	Antibiotic- associated AF (6/162) [22, 28, 60, 65, 66]	Corticosteroid-associated AF (2/162) [20, 75]	Interferon α2-associated AF (1/162) [94]	Androgen-associated AF (12/162) [51, 52, 70, 95-99, 100]	Miscellaneous AF (104/162) [4-10, 12, 14, 15, 16, 18, 21, 23, 24, 29-33, 35, 38-43, 45, 47, 48, 54, 55, 57, 62, 64, 65, 72, 78, 81-93]
Cutaneous lesions						
Ulcerations and erosions	26 [2, 13, 17, 19, 25-27, 34, 36, 44, 53, 59, 60, 61, 63, 68, 69, 70, 71, 73, 74, 76, 79, 80]	3 [22, 60, 66]	0	0	5 [52, 70, 95, 96, 99]	53 [5, 8-12, 14, 16, 18, 21, 23, 30, 38, 40-43, 48, 55, 64, 81, 83, 84, 86-90, 92]
Nodules	21 [2, 13, 34, 37, 46, 49, 50, 53, 56, 59, 60, 63, 68, 71, 74, 76, 77, 80]	2 [28, 66]	2 [20, 75]	0	8 [95-99, 100]]	29 [4, 7, 10, 12, 14, 18, 21, 23, 24, 33, 43, 54, 57, 62, 64, 72, 78, 81, 86, 89, 90-93]
Crusted and haemorrhagic lesions	18 [2, 17, 27, 36, 44, 49, 50, 53, 56, 60, 69, 70, 74, 76, 79, 80]	2 [28, 60]	2 [20, 75]	1 [94]	3 [70, 95, 100]	23 [4, 6, 11, 12, 14, 21, 30, 32, 33, 38, 48, 55, 57, 64, 72, 81, 83, 84, 86-88]
Cysts	13 [13, 25, 26, 34, 46, 49, 53, 60, 68, 74, 80]	0	1 [20, 75]	0	6 [52, 95, 98, 99, 100]	20 [4, 6, 7, 9, 10, 15, 21, 23, 24, 32, 33, 45, 62, 64, 81, 89, 91-93]
Papulopustular lesions	11 [13, 27, 37, 50, 53, 67, 69, 71, 76, 79]	1 [22]	2 [20, 75]	1 [94]	4 [96, 98, 99, 100]	22 [4, 7, 9, 11, 12, 14, 16, 18, 24, 29, 32, 40, 54, 55, 57, 64, 72, 83, 84, 88, 90-92]
Comedones	3 [67, 69, 76]	1 [60]	0	0	1 [99]	20 [5, 7, 9,23, 24, 29, 32, 62, 64, 65, 72, 78, 81, 83, 84, 89, 92, 93]
Necrosis	3 [19, 37, 61]	0	0	0	2 97	10 [9, 14, 31, 32, 39, 48, 64, 86, 89, 100]
Scars	3 [27, 63, 79]	1 [28]	0	0	0	2 [32, 54]
Painful acne	4 [53, c]	1 [60]	0	0	2 [51, 99]	29 [8, 35, 47, 62, 64, 65, 82, 85]
Systemic symptoms	28/39	3/6	½	1/1	9/12	84/104
Arthralgia	21 [2, 13, 17, 19, 25, 27, 36, 37, 46, 49, 53, 56, 60, 63, 70, 71, 73, 77, 79]	1 [66]	1 [20]	1 [94]	7 [51, 70, 95, 96, 98]	54 [4, 6-9, 11, 15, 16, 21, 23, 24, 29, 32, 33, 38, 41-43, 45, 48, 54, 55, 57, 62, 64, 65, 78, 81-86, 90-92]
Weight loss	20 [2, 17, 19, 25, 27, 34, 36, 37, 44, 46, 49, 53, 56, 58, 69, 71, 73, 79]	2 [28, 66]	1 [20]	1 [94]	4 [51, 95]	54 [6-12, 16, 18, 21, 23, 24, 29, 32, 33, 38, 40, 41-43, 55, 57, 62, 64, 78, 81-83, 86-93]

Fever	6 [2, 25, 28, 37, 44, 46, 60]	1 [60]	0	1 [94]	1 [96]	29 [6, 8, 10, 11, 24, 30, 35, 42, 43, 48, 62, 64, 72, 81-83, 87, 92]
Myalgia	5 [13, 34, 49, 53, 56]	0	0	1 [94]	0	22 [6, 15, 23, 24, 30, 32, 35, 40, 41, 43, 48, 55, 64, 82, 90, 92]
Osteolytic bone lesions	2 [13, 49]	0	0	0	0	18 [6, 23, 35, 38, 39, 41, 42, 48, 54]
Malaise	4 [17, 27, 53, 56]	2 [28, 66]	0	0	3 [96, 97]	17 [4, 9, 11, 12, 23, 24, 29, 32, 35, 41, 42, 48, 72, 78, 81, 83, 86, 87, 91]
Arthritis	6 [17, 41, 49, 58, 61, 69]	0	0	0	0	9 [8, 10, 30, 33, 47, 57, 87]
Lymphadenopathy	2 [2, 37]	0	0	0	1 [96]	4 [11, 29, 43, 48]
Hepatosplenomegaly	0	0	0	0	0	3 [24, 40, 43]
Tachycardia	0	0	0	0	0	1 [82]
Myositis	0	0	0	0	0	1 [31]
Osteomyelitis	0	0	0	0	0	1 [9]
Abdominal pain	1 [79]	1 [60]	1 [20]	0	0	1 [40]
Systemic illness	7/39	1/6	½	1/1	2/12	12/104
EN	3 [36, 50]	0	0	0	0	2 [43, 82]
SAPHO	2 [26, 54]	0	0	0	0	4 [47, 54, 90, 93]
Posterior scleritis and PG-like reaction	0	0	0	0	0	1 [12]
Crohn disease	0	0	0	0	0	1 [86]
RCU	0	0	0	0	0	1 [91]
Wegner syndrome	0	0	0	0	0	1 [78]
HS	1 [73]	1 [28]	0	0	0	1 [81]
Pyogenic granuloma-like lesions	1 [37]	0	0	0	0	0
Marfan syndrome	0	0	0	0	1 [52]	0
Adrenal hyperplasia	0	0	0	0	1 [51]	0
Idiopathic thrombocytopenic purpura	0	0	1 [22]	0	0	0
HBV	0	0	0	194	0	0
Laboratory findings	29/39	3/6	2/2	1/1	11/12	73/104
Leucocytosis	27 [2, 13, 17, 19, 25, 26, 27, 34, 36, 37, 44, 46, 49, 50, 56, 58, 61, 63, 70, 71, 73, 77, 79]	3 [60, 66]	2 [20, 75]	1 [94]	7 [51, 52, 70, 95, 96, 98]	62 [4, 6-9, 12, 15, 18, 21, 23, 24, 29, 30, 31-33, 35, 39, 40, 42-44, 48, 55, 57, 64, 65, 72, 78, 82-84, 86, 88-93]

Increased ESR	23 [2, 17, 19, 25, 26, 34, 36, 37, 44, 46, 49, 50, 56, 61, 63, 67-71, 73, 76, 77]	3 [28, 60, 66]	1 [20]	0	8 [51, 52, 70, 95, 96, 98]	29 [7-9, 11, 12, 15, 30-32, 35, 39-41, 64, 78, 83, 86, 87, 91-93]
Increased CRP	18 [17, 19, 25-27, 46, 49, 56, 58, 61, 63, 70, 73, 76, 79, 80]	2 [28, 60]	1 [20]	1 [94]	3 [52, 70, 96]	35 [12, 15, 16, 18, 21, 23, 64, 65, 72, 78, 91-93]
Neutrophylia	15 [2, 13, 17, 26, 27, 36, 37, 44, 46, 63, 71, 79]	0	0	0	0	23 [6, 7, 10, 11, 15, 16, 18, 21, 23, 31-33, 35, 45, 48, 57, 64, 82, 84, 87-89, 91-93]
Anaemia	5 [2, 34, 36]	0	0	0	2 [52, 95]	21 [4, 6, 7, 8, 12, 24, 30-33, 35, 42, 43, 45, 48, 55, 64, 89, 90, 91]
Increased alkaline phosphatase	0	0	0	0	0	6 [4, 6, 12, 30, 42, 43, 86]
Increased α1 in serum protein	0	0	0	0	0	4 [82, 83, 84, 88]
Increased α2 in serum protein	1 [34]	0	0	0	0	2 [7, 84]
Trombocytosis	3 [19, 61, 79]	0	0	0	0	2 [7, 89]
IgG immunocomplexes	3 [36, 44]	0	0	0	0	2 [40, 88]
Gamma-glutamyltrans-ferase	0	0	0	0	0	1 [6, 12]
Increased CPK	0	0	0	0	0	1 [86]
Increased urine albumin	0	0	0	0	0	1 [86]
Elevated LDH	0	0	0	0	0	1 [35]
Microscopic haematuria	1 [2]	0	0	0	0	1 [39]
Mielo/monocytosis	0	0	0	0	0	1 [12]
Positive FR	0	0	0	0	0	1 [12]
Increased C3	0	0	0	0	0	1 [93]
Increased ferritin	0	0	0	0	0	1 [64]
Increased transaminases	2 [58, 79]	0	1 [20]	1 [94]	0	0
Ipergamma serum protein	1 [61]	0	1 [20]	0	0	0

AF: acne fulminans; EN: erythema nodosum; SAPHO: synovitis acne pustulosis hyperostosis osteitis; PG: pyoderma gangrenosum; HS: hidradenitis suppurativa; HBV: hepatitis B virus; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; FR: rheumatoid factor; RCU: ulcerative colitis.

retinoids (36.84%) and systemic antibiotic therapy (34.21%). The other therapies are reported in *table 2*. The time taken for AF to resolve was reported for 28 of the 39 patients and their lesions improved after an average of 6.4 months and a median of four months.

Antibiotic-associated AF (*table 1*)

Among six patients with antibiotic-associated AF, ulcerations and erosions were the most reported skin lesions in three patients. Images of a patient with AF associated with lymecycline treatment are presented in *figure 2*. Systemic symptoms, in particular malaise and weight loss, were reported in two of six patients.

Three patients did not show any systemic symptoms. One patient reported an association between AF and HS. Laboratory anomalies were observed in three of six patients, in particular, leukocytosis and increased ESR. All patients received systemic corticosteroids and systemic retinoids (*table 2*).

Table 2. Therapies of patients with AF secondary to systemic treatment (isotretinoin-associated AF, antibiotic-associated AF, corticosteroid and interferon α2-associated AF), high androgen levels, and miscellaneous factors.

Systemic treatment associated to AF						
	Isotretinoin-associated AF (39/162) [2, 13, 17, 19, 25, 26, 27, 34, 36, 37, 44, 46, 49, 50, 53, 56, 58, 59, 61, 63, 67, 68, 69, 70, 71, 73, 74, 76, 77, 79, 80]	Antibiotic-associated AF (6/162) [22, 28, 60, 65, 66]	Corticosteroid-associated AF (2/162) [20, 75]	Interferon α2-associated AF (1/162) [94]	Androgen-associated AF (12/162) [51, 52, 70, 95-99, 100]	Miscellaneous AF (104/162)[[4-10, 12, 14, 15, 16, 18, 21, 23, 24, 29-33, 35, 38-43, 45, 47, 48, 54, 55, 57, 62, 64, 65, 72, 78, 81-93]
Systemic corticosteroids	29 [2, 13, 17, 19, 25, 27, 36, 44, 49, 50, 53, 56, 58, 59, 60, 61, 63, 67, 70, 71, 77, 80]	6 [22, 28, 60, 65, 66]	0	0	10 [51, 52, 70, 95-97, 99, 100]	69 [9, 12, 14, 15, 16, 18, 21, 23, 29, 30, 32, 39-41, 43, 45, 48, 49, 54, 55, 64, 65, 72, 78, 84, 86, 88, 89, 91]
Systemic retinoids	14 [2, 13, 19, 25, 37, 46, 50, 59, 60, 61, 71, 77]	6 [22, 28, 60, 65, 66]	1 [20]	1 [94]	8 [51, 95, 96, 97, 99]	41 [4, 5, 10, 15, 18, 21, 23, 29, 39, 40, 43, 45, 48, 54, 57, 65, 78, 89, 93]
Systemic antibiotics	13 [2, 13, 19, 25, 37, 46, 50, 59, 61, 77]	0	2 [20, 75]	0	5 [52, 70, 96, 98, 99]	29 [2, 4, 6, 7, 9, 11, 18-20, 23, 24, 26, 35, 38-40, 43, 44, 48, 49, 52, 54, 57, 58, 64, 70, 72, 73, 76, 82, 86, 93, 96, 98]
Dapsone	3 [27, 50, 74]	0	0	0	1 [52]	6 [9, 11, 31, 55, 57, 91]
Biologic therapies	5 [26, 63, 69, 79]	0	0	0	0	4 [24, 26, 63, 69]
Immunosuppressive therapies	2 [49, 61]	0	0	0	0	4 [18, 21, 49, 78, 88]
Topical benzoyl peroxide	1 [56]	0	0	0	2 [96, 99]	6 [4, 11, 33, 39, 57, 93]
NSAIDs/opioids	0	0	0	0	0	3 [4, 11, 33]
Topical steroids	2 [66, 68]	0	0	0	0	2 [4, 39]
Topical retinoids	0	0	0	0	0	1 [6]
Topical antibiotics	2 [76]	0	1 [20]	0	0	1 [93]
Debridement	0	0	0	0	0	1 [5]
Colchicine	0	0	0	0	0	1 [93]
Other topical treatments	0	0	0	0	0	3 [4, 11, 33]
Photodynamic therapy	1 [80]	0	1	0	0	0

AF: acne fulminans; NSAIDs: non-steroidal anti-inflammatory drug.

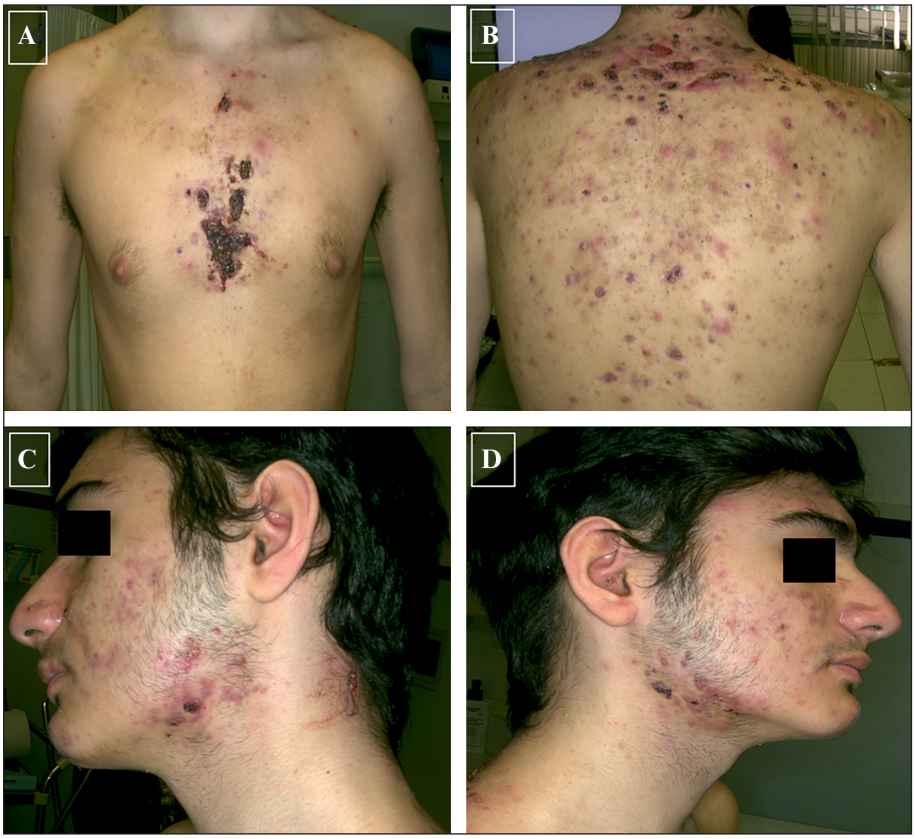

Figure 2. Lymecycline-induced AF with inflammatory papules, nodules and cysts on the chest (**A**), back (**B**), and face (**C**, **D**) at baseline.

The time taken for AF to resolve was reported for five of six patients, and lesions improved after an average of seven months and a median of three months.

Corticosteroid and interferon α2-associated AF (*table 1*)

Among three patients with corticosteroid and interferon α2-associated AF, all presented with crusted and haemorrhagic lesions and papules and pustules. Systemic lesions were reported in two of three patients, in particular, arthralgia and weight loss. All of the three patients presented with leucocytosis. Administered therapy was reported for all three patients (*table 2*). Overall, systemic retinoids and systemic antibiotics were the most frequently used treatments in two of three patients.
The time taken for AF to resolve was reported for all patients, and their lesions improved after a mean of six months and a median of three months.

Androgen-associated AF (*table 1*)

Twelve of 162 patients presented with AF associated with high levels of androgens, and of these, four were taking testosterone for bodybuilding [70, 96, 98, 100] before developing AF, six had a history of a genetic syndrome associated with testosterone therapy (Kallmann's syndrome, Marfan's syndrome, tall boy) [52, 95, 97] one was a genetic case with increased androgen (adrenal hyperplasia) [51] and one was taking testosterone for modify secondary sexual characteristics [99]. These patients were labelled "androgen-associated AF". AF induced by higher levels of androgens more frequently presented with nodules (8/12) and cysts (6/12) than papules and pustules (4/12), crusted and haemorrhagic lesions (3/12), and necrosis (2/12). Only one patient had comedones. Systemic symptoms were reported in 9 of 12 patients; in particular, arthralgia in 7 of the 12 patients. The most frequent anomalies based on laboratory examinations were increased ESR and leukocytosis in 8 and 7 of 12 patients, respectively. Administered therapy was reported in all patients (*table 2*). Overall, 10 were treated with systemic corticosteroids and eight with systemic retinoids. Other treatments are reported in *table 2*.
The time taken for AF to resolve was reported in 10 of 12 patients, and their lesions improved after an average of 6.5 months and a median of four months.

Miscellaneous AF (*table 1*)

In the majority of cases, AF was not associated with any apparent cause (104/162; 64.2%). This group was classified as "miscellaneous AF", and presented, in particular, with ulcerations and erosions (50.96%), nodules (27.88%), and painful acne (27.88%).
Systemic symptoms were reported in 84 of 104 patients, notably arthralgia (51.92%) and weight loss (51.92%).

AF was associated with systemic illness in 12 of 104 patients, notably SAPHO in four patients. Seventy-three patients of 104 had laboratory anomalies. The most frequent laboratory anomalies were leucocytosis (59.6%) and increased CRP (33.65%).
Administered therapy was reported in 85 of 162 patients (*table 2*). Overall, 69 were treated with systemic corticosteroids (81.17%), systemic retinoids (48.23%) and systemic antibiotics (34.11%). Other treatments are reported in *table 2*.
The time taken for AF to resolve was reported in 62 of 104 patients, and lesions improved after an average of 5.05 months and a median of four months.

Discussion

In the literature, there are no reviews that compare clinical appearance, laboratory anomalies and therapies among patients with AF following systemic treatment, patients with a high level of androgen, or patients with miscellaneous factors.
Commonly, all cases of AF were characterized by sudden onset of severe lesions such as erosions and painful haemorrhagic crusts associated with lesions of severe acne such as nodules, cysts, multiple papules, pustules, open and closed comedones, and acne scars [3, 101]. Although the clinical presentation appeared to be similar among all the cases of AF, our review highlights some differences. AF induced by high levels of androgens more frequently presented with nodules and cysts than erosions, crusted and haemorrhagic lesions, and necrosis. Nodules and cysts may be due to higher doses of testosterone or anabolic-androgen steroids (AAS) (testosterone enanthate, trenbolone acetate, drostanolone proprionate, and methandrostenolone), which are reported to increase the size of sebaceous glands, sebum production, and *P. acnes* density [95]. In contrast, patients affected by miscellaneous AF more frequently presented with ulcerations and erosions, and patients with AF associated with acne treatment showed a similar frequency of ulcerations, erosions, nodules, and crusted and haemorrhagic lesions. Moreover, patients with AF associated with systemic treatment for other diseases reported a higher frequency of crusted and haemorrhagic and papulopustular lesions. Since AF associated with systemic treatment positively correlated with a history of previous acne vulgaris (47/48), this may explain the similar frequency of lesions of acne vulgaris (*e.g.*, nodules, papules, pustules), ulcerations, erosions and haemorrhagic lesions in AF patients.
In the literature, open and closed comedones were reported as rare and without significance [3, 102-104]. According to the literature, we found comedones in a discrete number of patients, notably, in only 1/12 patients affected by androgen-associated AF and in 1/6 patients with AF associated with antibiotics. AF associated with androgens is probably rarely linked to previous acne vulgaris, and consequently, comedones were infrequent in these AF patients.
Regarding systemic symptoms, these occurred with a similar frequency in patients with different forms of AF with the exception of those with osteolytic lesions which were more frequent in patients with miscellaneous AF (18/104). The pathogenetic relationship between acne and osteolytic lesions or arthritis is uncertain. Although in one case, *Propionibacterium* was found [105], in all other described cases, cultures of cutaneous pus, blood and bone marrow were negative, excluding an infective aetiology. Curiously, only half of the patients with AF associated with antibiotics had systemic symptoms, of whom only one had arthralgia, which was the most frequent systemic symptom reported for all other forms of AF.
Patients with AF can also have systemic illness (*e.g.*, adrenal hyperplasia, measles) which may or may not be linked to the skin lesions. In miscellaneous cases, AF was more frequently associated with other autoimmune diseases such as EN, Crohn disease and ulcerative colitis (RCU), and was a clinical manifestation of SAPHO. EN more frequently correlated with isotretinoin-associated AF, and circulating immune complexes have been considered to be involved in the pathogenesis.
Commonly retrieved laboratory abnormalities reported in AF included leucocytosis and increased ESR and CRP. In particular, leucocytosis similarly increased in patients with AF associated with systemic treatment and miscellaneous AF. On the other hand, an increase in ESR and CRP was more frequently reported in cases of AF associated with systemic treatment than miscellaneous AF. In contrast, an increase in alkaline phosphatase and increase in α1 in serum protein were only reported in patients affected by miscellaneous AF. The increased neutrophil rate was especially evident in miscellaneous AF and AF induced by isotretinoin; in the latter, the drug significantly increases the metabolic burst from peripheral neutrophils. Similarly, as for systemic symptoms, laboratory anomalies were found in only three of six patients with AF associated with antibiotics: these two findings led us to consider a different pathogenic pathway relative to other forms of AF.
Currently, primary treatment options for AF are systemic corticosteroids (prednisolone or prednisone), retinoids (isotretinoin), and systemic antibiotic treatment (doxycycline 100 mg twice daily, minocycline 100 mg twice daily, tetracycline 500 mg to 1 g twice daily). Regarding associated factors in the literature, we noticed that treatments for AF were different, notably for AF associated with systemic treatment. In fact, systemic corticosteroid and systemic retinoid therapy were preferred for antibiotic-associated AF, while systemic corticosteroids were more frequently prescribed for isotretinoin-associated AF and miscellaneous AF. Additionally, systemic antibiotics and isotretinoin were preferred in patients with steroid-induced AF and, as expected, corticosteroid-associated AF.
Immunomodulatory drugs were reported as AF therapy, especially in miscellaneous AF. Dapsone can be used as monotherapy when corticosteroids or isotretinoin are contraindicated, or in cases of AF associated with autoimmune diseases such as EN or RCU [50, 91]. The indicated dose is 50-75 mg/day, rarely 100-200 mg/day up to 12 months [74], or in combination with prednisolone or isotretinoin [50]. However, we advise caution in prescribing dapsone for AF; a case of AF treated with dapsone and complicated by haemolysis has been

reported in the literature [11] Immunosuppressive agents have been used in combination with systemic prednisolone or isotretinoin in selected cases of miscellaneous AF. In AF with pyoderma gangrenosum-like ulcerations, cyclosporine A (5 mg/kg/day) has been used in combination with prednisolone (10-40 mg/day) or isotretinoin (30 mg/day) [21]. Cyclosporine A is considered safe because it has a very good short-term safety profile (particularly in young patients) [21]. In cases of severe skeletal involvement, the use of methotrexate (15 mg/weekly with folic supplementation up to 12 months) [61] may be recommended following corticosteroid tapering [61]. For musculoskeletal symptoms, salicylate may be prescribed. In AF with circulating immune complexes and leukemoid reaction, azathioprine (1-3 mg/kg/day for eight months) may be combined with corticosteroids [68]. The use of immunosuppressive agents is based on disease similarities among various forms of AF and recently described autoinflammatory entities such as SAPHO syndrome [54]. In cases of AF unresponsive to conventional therapies or with severe articular involvement, with either SAPHO syndrome or HS [81], therapy may be prescribed with recombinant IL-1 receptor antagonist (anakinra) [63] or tumour necrosis factor-α (TNF-α) inhibitors (infliximab, adalimumab) [81]. Anti-TNFα has been shown to be useful, not only for inflammatory lesions, but also for comedogenesis. This could be explained by the effect of TNF-α on follicular hyperkeratinisation and induction of lipogenesis [46]. In one reported case without severe systemic involvement, the patient was treated with photodynamic therapy with 5-aminolevulinic acid (ALA-PDT) in combination with systemic isotretinoin to limit systemic antibiotic use [75]. ALA-PDT was set with red light (635 nm) at 100 mw/cm^2 irradiance for 20 min after three hours of occlusion with 20% ALA on the entire area involved. The authors suggested that this combined approach may be useful to achieve rapid clearance of lesions and lower doses of tretinoin.

Topical treatments could be used as adjunctive therapies; the most frequent therapies are benzoyl peroxide and antibacterials (erythromycin and fusidic acid). Topical steroids can reduce inflammation and can be applied to erosions of granulation tissue, especially isotretinoin and for miscellaneous AF.

In this review, we have investigated clinical and laboratory differences among AF secondary to systemic treatment, high androgen levels and miscellaneous factors. In conclusion, our review highlights that, even though AF may appear identical in all cases during preliminary examination, it may vary slightly regarding clinical features, laboratory anomalies, and associated systemic illnesses, and these aspects should be evaluated in order to plan a personalized therapeutic scheme. We suggest a classification of AF according to its association with certain factors. ■

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