Αυτοάνοσες διαταραχές με τη χρήση βιολογικών παραγόντων

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Outline

- Introduction
- Autoimmune phenomena
  - Autoimmune diseases
  - Paradoxical inflammation
- Our experience
- Conclusions

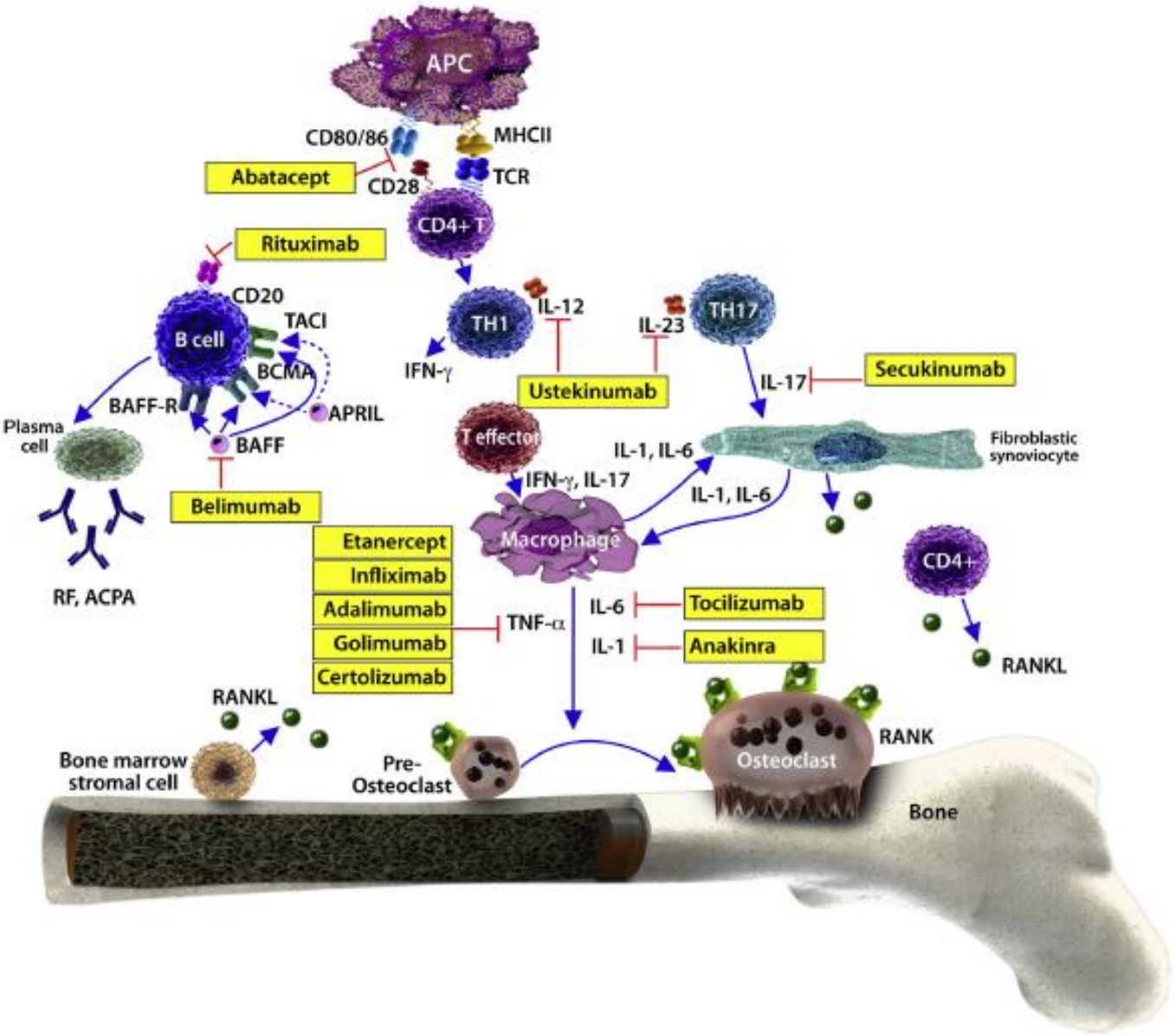
Biologic agents in rheumatology (I)

- Biologic agents have revolutionized the treatment of a number of systemic inflammatory and autoimmune diseases including: RA, SpA, PSO, IBD

TABLE I. Biologic agents for RA and other rheumatic diseases

Target	Agent	Structure	FDA approval
Cytokine			
TNF-α	Etanercept	Soluble TNF receptor IgG Fc fusion protein	AS, JIA, PsA, PsO, RA
	Infliximab	Chimeric anti–TNF-α mAb	AS, CD, PsA, PsO, RA, UC
	Adalimumab	Fully human anti–TNF-α mAb	AS,CD,JIA, PsA, PsO, RA, UC
	Golimumab	Fully human anti–TNF α mAb	AS, PsA, RA, UC
	Certolizumab pegol	Humanized Fab′ fragment linked to pegylated molecules	AS, CD, PsA, RA
IL-1 receptor	Anakinra	Recombinant IL-1 receptor antagonist	CAPS, RA,
IL-6 receptor	Tocilizumab	Humanized anti–IL-6 receptor mAb	JIA, RA
IL-12/IL-23	Ustekinumab	Fully human anti–IL-12/IL-23 mAb	PsA, PsO
IL-17	Secukinumab	Fully human anti–IL-17A mAb	PsO
Lymphocyte			
T cell			
CD28	Abatacept	CTLA-4:Ig G Fc fusion protein	RA, JIA
B cell			
CD20	Rituximab	Chimeric anti-CD20 mAb	CLL, NHL, RA, GPA, MPA
BAFF	Belimumab	Fully human mAb for soluble BAFF	SLE

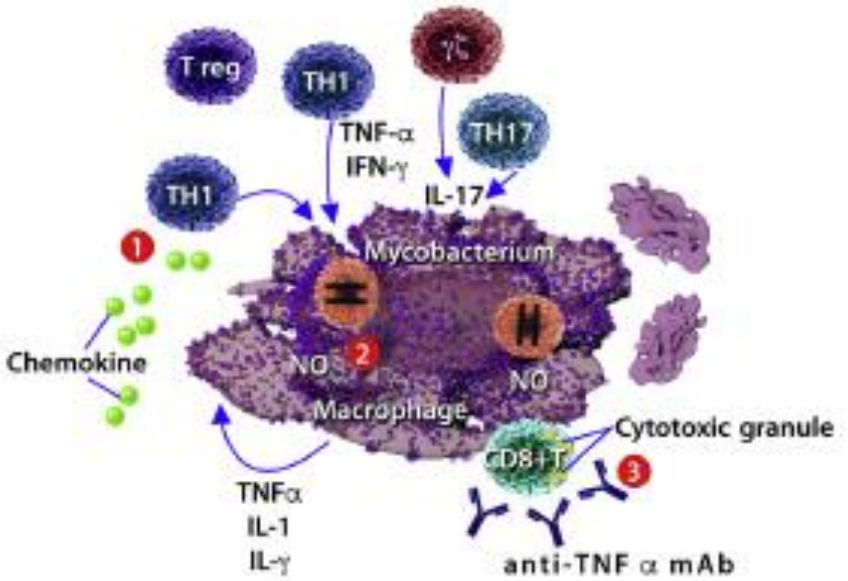
Her M, et al. J Allergy Clin Immunol. 2016;137:19-27

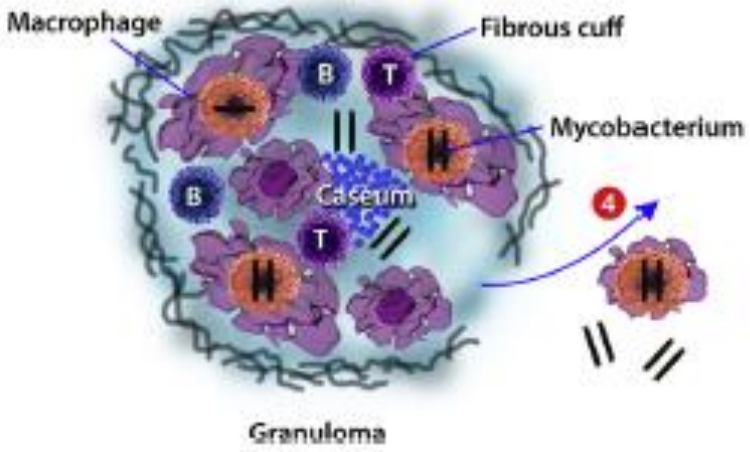


Her M, et al. J Allergy Clin Immunol. 2016;137:19-27

Biologic agents in rheumatology (IV)

- However, all these targets are key components of normal immune homeostasis and involved in a array of normal physiologic responses. Therefore, blocking particular cytokines or cells might result in adverse events

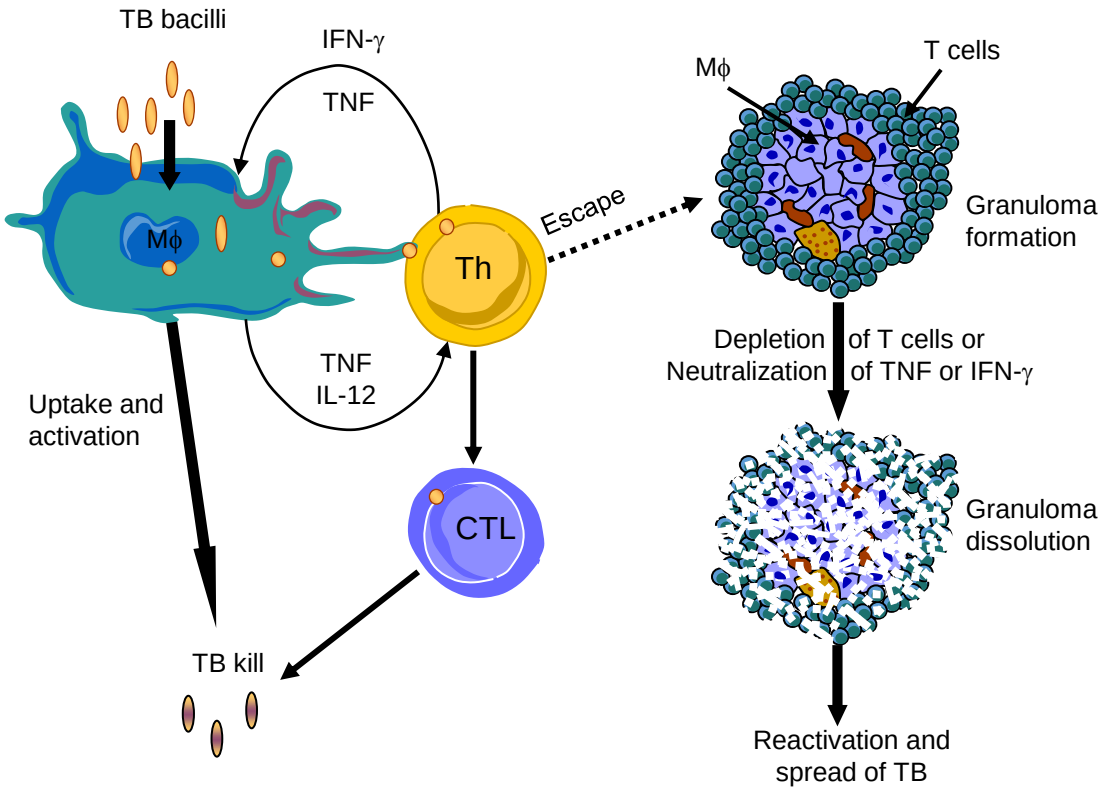




Her M, et al. J Allergy Clin Immunol. 2016;137:19-27

TNF-α plays a key role in host defense and autoimmunity

- TNF-α is a key cytokine driving inflammation in RA[1]
- TNF-α is involved in host defence from intracellular pathogens[2]



Choy and Panayi. NEJM 2001; 344:907-916
Quesniaux et al. Curr Dir Autoimmun 2010;11:157-179

Her M, Kavanaugh A

Alterations in immune function with biologic therapies for autoimmune disease

J Allergy Clin Immunol. 2016;137:19-27

Biological agents and autoimmunity

- Autoantibody and autoimmune diseases
- Paradoxical inflammation

Autoantibody and autoimmune diseases

Biological agents induce autoimmune manifestations ranging from an isolated presence of an autoantibody

- ANA
- Full-blown autoimmune diseases
  - SLE, anti PLs, vasculitis, demyelinating disorder inflammatory ocular diseases

Autoimmune diseases related to biologic agents

- Organ specific
  - ILD
  - Uveitis
  - Optic neuritis
  - Peripheral neuropathies
  - MS
  - IBD, etc.
- Systemic
  - SLE
  - Vasculitis
  - Inflammatory myopathies
  - Sarcoidosis
  - Antiphospholipid syndrome, etc.

Occurrence of autoantibodies and lupus

ANA anti dsDNA and anti PLs antibodies are more frequency detected

180 pts with IBD treated with INF

- ANA positivity 49%
- dsDNA 10%
- SLE 9%
- Severe SLE 1%

Beigel F, et al. Inflamm Bowel Dis 2011;17:91-8

Occurrence of autoantibodies and lupus

France registry

7700 pts treated with INF

- 0,19% SLE

3800 pts treated with ETN

- 0,18 SLE

De Bandt M, et al. Arthritis Res Ther. 2005;7:R545-51

Occurrence of anti PLs antibodies

- Anti PLs 7% - 11%
- Antiphospholipid syndrome 1%

Boyman O, et al. Nat Rev Rheumatol 2014;10:612-27

REV BRAS REUMATOL. 2013;53(4):358–364

ELSEVIER

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Artigo de revisão

Revisão sistemática da indução de autoanticorpos e lúpus eritematoso pelo infliximabe☆

João Luiz Pereira Vaz[a,b,*], *Carlos Augusto Ferreira Andrade*[c], *Alessandra Cardoso Pereira*[a,d], *Maria de Fátima M. Martins*[e], *Roger Abramino Levy*[a]

Tabela 2 – Variação dos autoanticorpos antes e após o uso de infliximabe

Autoanticorpo	n	Antes do tratamento	Após o tratamento	Variação (%)
FAN	695	199 (28,6%)	469 (67,5%)	38,9
Anti-DNAds	669	8 (1,2%)	117 (17,5%)	16,3
Anti-ENA total	351	0	0	0
aCL	222	21 (9,5%)	49 (22%)	12,5
Anti-β2GP1	74	0	6 (8,1%)	8,1
Anti-histona	388	48 (12%)	116 (30%)	18
Antinucleossomo	147	9 (6,1%)	22 (15%)	8,9
M ANCA	108	0	7 (6,5%)	6,5

FAN, fator antinuclear; anti-DNAds, anti-DNA nativo ou dupla hélice; anti-ENA, antígenos extraíveis pela salina; aCL, anticardiolipina; anti-β2GP1, anticorpo anti-β 2 glicoproteína 1; ANCA, anticorpos contra citoplasma de neutrófilos.

Vaz JL, et al. Rev Bras Reumatol 2013;53:358-64

Autoimmunity Reviews 9 (2010) 188–193

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Autoimmune diseases induced by biological agents
A double-edged sword?

Manuel Ramos-Casals [a,*], Roberto-Perez-Alvarez [b], Candido Diaz-Lagares [a], Maria-Jose Cuadrado [c], Munther A. Khamashta [c] and BIOGEAS Study Group [1]

Table 1
Characteristics of the main autoimmune diseases associated with biological agents (BIOGEAS Registry, last update July 15, 2009).

	Reported cases (*n*)	Mean age ± SEM (years)	Female (%)	Underlying disease: RA, Sp, IBD (%)	Biological agent: INF, ETA, ADA, other (%)
a) Systemic autoimmune diseases					
• DIL	140	49.51 ± 1.68	77	72, 7, 11	37, 33, 25, 6
• Vasculitis	139	51.55 ± 2.68	79	92, 7, 8	43, 42, 7, 7
• APS/APS-like disease	42	50.00 ± 3.79	70	26, 11, 26	45, 41, 5, 9
• Sarcoidosis	38	49.41 ± 2.05	65	60, 37, 0	26, 61, 10, 3
b) Organ-specific autoimmune diseases					
• Optical neuritis[a]	123	43.47 ± 3.29	63	37, 17, 25	43, 49, 7, 1
• Interstitial lung disease	118	62.79 ± 1.98	77	77, 6, 4	43, 47, 3, 7
• Inflammatory ocular disease	87	45.96 ± 2.16	81	41, 48, 0	18, 79, 2, 0
• MS/MS-like[a]	55	42.83 ± 1.99	70	59, 17, 12	20, 51, 27, 2
• Peripheral neuropathies[b]	44	52.47 ± 2.16	66	61, 16, 16	74, 12, 14, 0
• Autoimmune hepatitis	19	45.24 ± 2.83	76	32, 47, 21	79, 10, 10, 0

Ramos-Casals M, et al. Autoimmun Rev 2010;9:188-93

Clinical manifestations of SLE due to biologic agents

- Arthralgia's, myalgia's
- Low great fever
- Cutaneous manifestations
- Photosensitivity
- Malar rash
- Discoid lupus
- Oral ulcer
- **While kidney disease and CNS are very uncommon**
- **Treatment:** stop of suspected agent, small dose of steroids and local steroids

Hypothesis to explain the production of autoantibodies and SLE like syndrome

- TNFs can induce cell apoptosis, causing release of antigenic material and the production of antibody
- Cytokine shift involving TNF and IFNs
  - Anti TNFs can interfere with Th1/Th2 response, suppressing Th1 response and favor Th2 cell and IFNs witch are involved in SLE pathogenesis
- Infection: causes by TNF inhibitors may induce SLE
  - Bacterial DNA with its immunostimulatory motifs, might help trigger autoantibody production in infection

Chang C, et al. Drug Saf 2011;34:357-74
D'Auria F, et al. J Inter Med 2004;255:409-18
Williams VL, et al. Int J Dermatol 2011;50:819-31
Wahren-Herlenins M, et al. Lancet 2013;382:819-31

DISEASE STATES

Drug-Induced Lupus due to Anti-Tumor Necrosis Factor α Agents

Michelle F. Costa, DO,* Nuha R. Said, MD,† and
Bernard Zimmermann, MD‡

Costa MF, Said NR, Zimmermann B

Drug-induced lupus due to anti-tumor necrosis factor alpha agents

Semin Arthritis Rheum. 2008;37:381-7

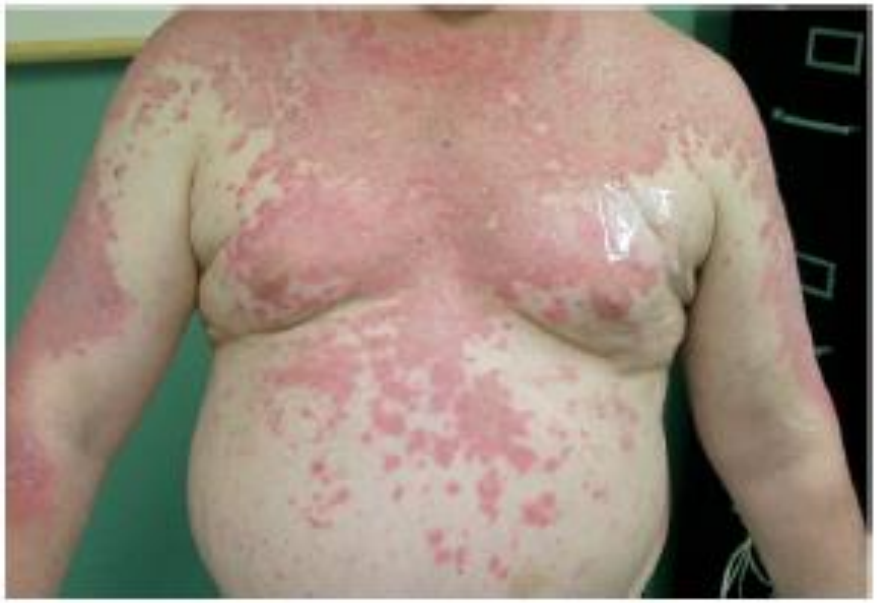


Figure 1 Extensive erythematous scaling rash on the trunk and arms of patient 2.

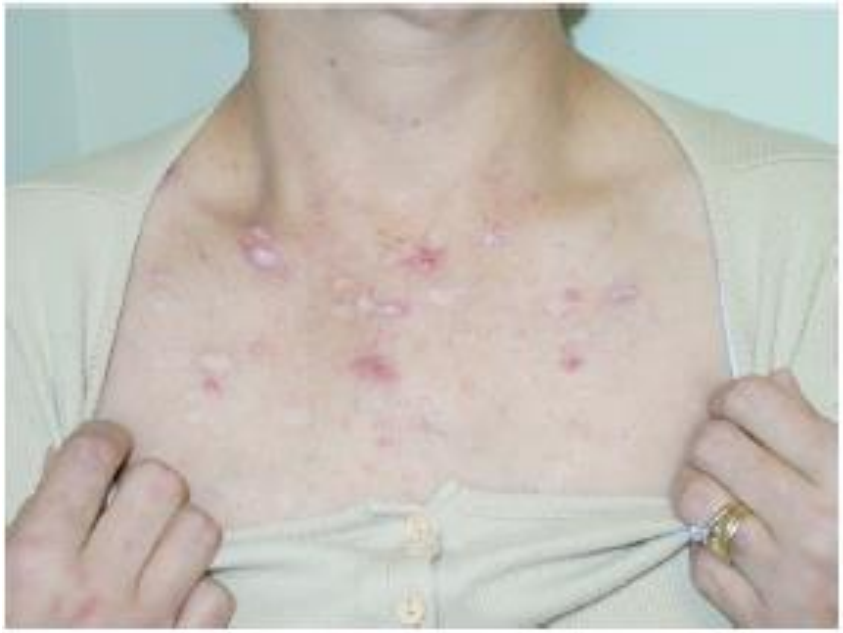


Figure 2 Discoid lesions in photosensitive distribution on the chest of patient 3.

Costa MF, et al. Semin Arthritis Rheum 2008;37:381-7

Table 1 Characteristics of 33 Case Reports of Anti-TNF DILE (4,10,13,17-30)

	No. (%) of Cases
Underlying Disease	
Rheumatoid arthritis	25 (76)
Juvenile idiopathic arthritis	3 (9)
Psoriatic arthritis	2 (6)
Crohn's disease	2 (6)
Ankylosing spondylitis	1 (3)
Drug	
Infliximab	21 (64)
Etanercept	10 (30)
Adalimumab	2 (6)

Costa MF, et al. Semin Arthritis Rheum 2008;37:381-7

Table 2 Clincal Features of 33 Case Reports of Anti-TNF DILE (4,10,13,17-30)

Clinical Manifestation	No. (%) of Cases
Rash	24 (73)
Polysynovitis	17 (52)
Fever	17 (52)
Myalgias	8 (24)
Pericardial/pleural effusion	3 (18)
Nephritis	3 (9)
Valvulitis	1 (3)
Pneumonitis	1 (3)
Deep vein thrombosis	1 (3)
Oral ulcers	1 (3)

Costa MF, et al. Semin Arthritis Rheum 2008;37:381-7

Table 3 Abnormal Laboratory Values of Case Reports (4,10,13,17-30)

Laboratory Test	Number of Positive Results	(Percent Positive Results)
ANA	32/32*	(100)
dsDNA	29/32	(91)
Hypocomplementemia	13/22	(59)
Anti-histone antibody	16/28	(57)
ENAs	10/19	(53)
Leukopenia	11/22	(50)
Thrombocyopenia	6/22	(27)
Lymphopenia	3/22	(14)

*Denominator, number of cases in which result was reported.

Costa MF, et al. Semin Arthritis Rheum 2008;37:381-7

Table 4 Reported Cases of Renal Involvement in Anti-TNF DILE

Reference	Age, Sex/ Diagnosis	Drug	Urinalysis	C3/C4	Positive Serology	Histone Antibodies	dsDNA	Biopsy
Carlson (9)	45, F/RA	Etanercept	8 to 10 RBCs	Low	Ro, La, Sm, RNP	NR	+	ND
Chadha (20)	34, F/RA	Infliximab	294 mg protein/ 24 h	Low	SSA, SSB, aCL IgM	+	+	ND
Mor (25)	22, F/JRA	Etanercept	3.6g protein/24 h, WBCs, 3+ RBCs, granular casts	Low	SSA, Sm	+	+	WHO Class IV
Stokes* (29)	30, F/JRA	Etanercept	7 g protein/24 h, RBC casts	Low	IgG aCL	NR	+	WHO Class IV
Stokes (29)	52, F/RA	Adalimumab and prior use of infliximab	3.8 g protein/24 h, RBCs, granular casts	Low	Atypical ANCA	NR	+	WHO Class III

NR = Not reported.
ND = Not done.
*This report included 3 other cases of vasculitis attributed to anti-TNFα therapy.

Costa MF, et al. Semin Arthritis Rheum 2008;37:381-7

Available online http://arthritis-research.com/content/7/3/R545

Research article

Open Access

Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey

Michel De Bandt[1], Jean Sibilia[2], Xavier Le Loët[3], Sebastian Prouzeau[4], Bruno Fautrel[5], Christian Marcelli[6], Eric Boucquillard[7], Jean Louis Siame[8], Xavier Mariette[9] and the Club Rhumatismes et Inflammation

De Bandt M, Sibilia J, et al.; Club Rhumatismes et Inflammation

Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey

Arthritis Res Ther. 2005;7:R545-51

Table 1

General presentation of the 10 patients with 'limited skin lupus' or toxiderma in a context of autoimmunity

Patient	Before anti-TNF alpha treatment				During onset of symptoms		
	Disease	Autoantibody	Clinical signs of lupus	Treatment	Duration of treatment (months)	Clinical signs of lupus	Biological signs of lupus
1	RA, erosive	RF+	None	ETA	36	Skin	ANA+, dsDNA+
2	RA, erosive	RF+	None	INF	6	Skin	ANA+, dsDNA+
3	RA, erosive	RF+, ANA+ 1:160*	None	INF	18	Skin	ANA+, dsDNA+
4	RA, erosive	RF-	None	ETA	5	Skin	ANA+, dsDNA+
5	RA, erosive	RF+	None	INF	7	Skin	ANA+, dsDNA+
6	RA erosive	RF+	None	ETA	5	Skin	ANA+, dsDNA+
7	RA, erosive	RF+	None	INF	11	Skin	ANA+, dsDNA+
8	RA, erosive	RF+	None	INF	3	Skin	ANA+, dsDNA+
9	RA, erosive	RF+	None	ETA	12	Skin	ANA+, dsDNA+
10	RA, erosive	RF+	None	INF	13	Skin	ANA+, dsDNA+

De Bandt M, et al. Arthritis Res Ther 2005;7:R545-51

Table 2

General presentation of the 12 patients with 'complete lupus'

Patient	Before anti-TNF alpha treatment					During onset of symptoms	
	Disease	Autoantibody	Clinical signs of lupus	Treatment	Duration of treatment (months)	Clinical signs of lupus[a]	Biological signs of lupus
1	RA, RF+, erosive	None	None	INF	27	General, skin, serositis, lung	ANA+, dsDNA+, ACL+, leucopenia, thrombopenia, ENA+
2	RA, RF+, erosive	ANA+, Ro+	None	INF	4	General, skin (3), arthritis	ANA+, dsDNA+, histone +
3	RA, RF+, erosive	ANA+, Ro+	None	INF	2	Skin, myalgias, arthritis	ANA+, dsDNA+, ENA+,
4	RA, RF-, erosive	None	None	ETA	4	General, skin (2), myositis	ANA+, dsDNA+, ACL+, low C4, ENA+
5	RA, RF+, erosive	None	None	INF	4	Skin (3), myositis, arthritis, pericarditis	ANA+, dsDNA+, ACL+, CPK, lymphopenia
6	RA, RF+, erosive	ANA+, dsDNA+ limit value	None	ETA	5	General, skin	ANA+, dsDNA+, thrombopenia, leucopenia
7	RA, RF+, erosive	None	None	INF	10	General, serositis, myositis	ANA+, dsDNA+, ACL+, leucopenia, thrombopenia, CPK,
8	RA, RF+	None	None	ETA	2	Phlebitis, skin	ANA+, dsDNA+, leucopenia, ACL+, thrombopenia
9	Psoriatic arthritis	None	None	INF	14	General, skin, neurological	ANA+, dsDNA+
10	RA, RF+, erosive	None	None	INF	16	General, Skin, arthritis	ANA+, dsDNA+
11	RA, RF+, erosive	None	None	INF	12	General, skin (3), arthritis, myositis	ANA+, dsDNA+, ENA+, CPK
12	RA, RF+, erosive	None	None	INF	10	General, skin, arthritis	ANA+, dsDNA+, CPK, ENA+, ACL+, low C4, histone+, leucopenia, lymphopenia, Coombs test+

De Bandt M, et al. Arthritis Res Ther 2005;7:R545-51

RHEUMATOLOGY

Rheumatology 2018;57:1896–1907
doi:10.1093/rheumatology/kex434
Advance Access publication 8 January 2018

Review

Drug safety and immunogenicity of tumour necrosis factor inhibitors: the story so far

Meghna Jani[1,2], William G. Dixon[1,2,3,4] and Hector Chinoy[2,3]

TABLE 1 Lupus and vasculitis-like events on TNFi agents reported to the UK regulatory agency

Drug (licensing date UK for RA)	Earliest reported event to MHRA	Reported LLE cases (*n*)	Reported vasculitis cases (*n*)
Infliximab (2002)	23 July 1999	Lupus-like syndrome (63) SLE (32) Cutaneous lupus (3)	Vasculitis (29) ANCA-+ve vasculitis (2) Cerebral vasculitis (2) Vasculitic rash (8) Granulomatosis with Polyangiitis (1) Bechet's syndrome (1) DM (1)
Etanercept (2002)	30 September 1999	Lupus-like syndrome (7) SLE (15) Cutaneous lupus (13) Lupus vasculitis (2)	Vasculitis (21) Necrotising vasculitis (2) Granulomatosis with Polyangiitis (1) Bechet's syndrome (1)
Adalimumab (2007)	24 March 2000	Lupus-like syndrome (25) SLE (25) Cutaneous lupus (11)	Vasculitis (24) Cutaneous vasculitis (11) Necrotising vasculitis (2) Gastrointestinal vasculitis (2) Cerebral vasculitis (2) Granulomatosis with Polyangiitis (1) Bechet's syndrome (5)
Certolizumab (2010)	25 February 2010	Lupus-like syndrome (3) Cutaneous lupus (1)	Vasculitis (1) Skin vasculitis (1) Panniculitis (1)
Golimumab (2011)	3 December 2010	Lupus-like syndrome (3) SLE (6)	Vasculitis (3) Skin vasculitis (1)

Jani M, et al. Rheumatology (Oxford) 2018;57:1896-1907

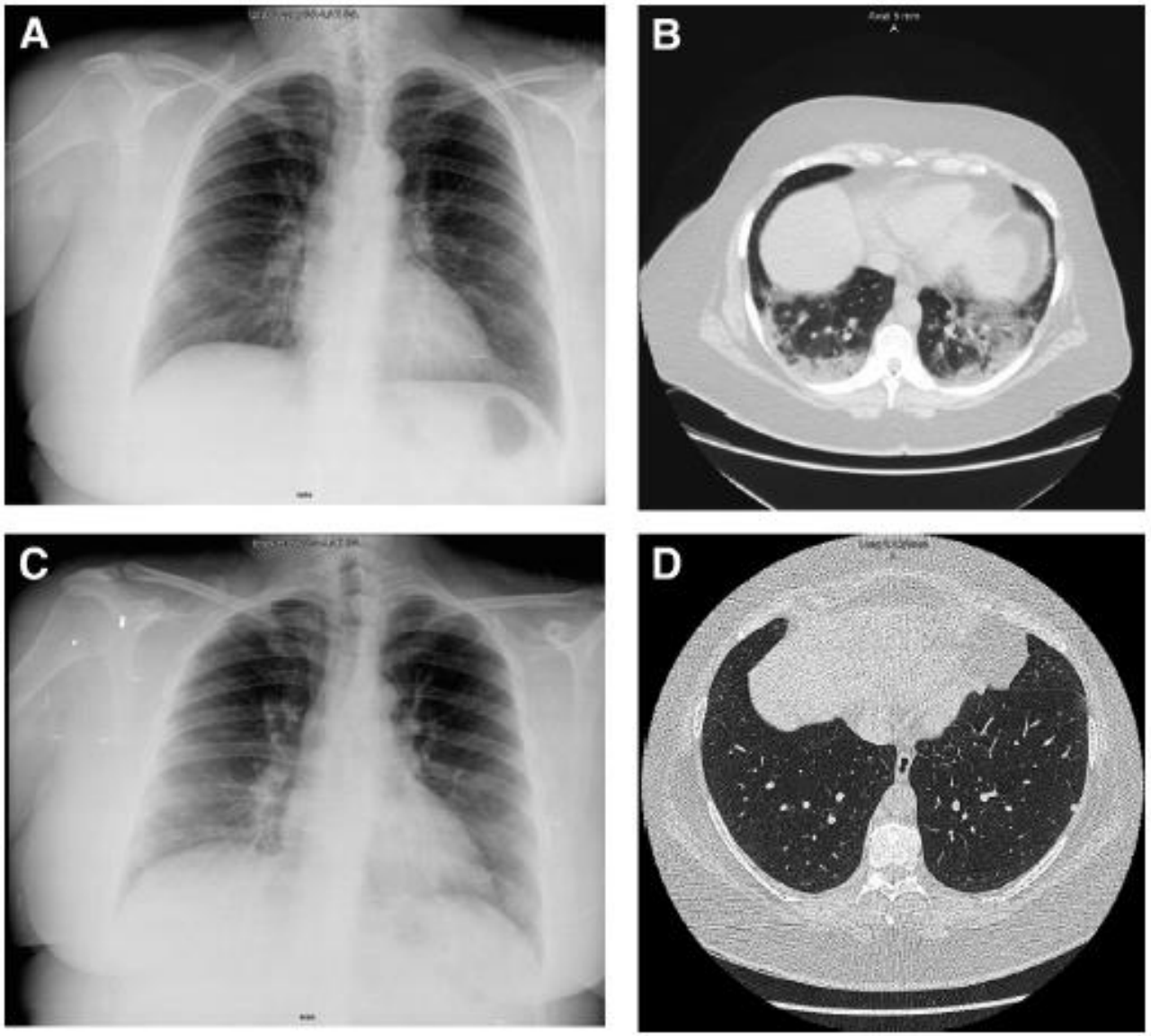
Interstitial Lung Disease Induced or Exacerbated by TNF-Targeted Therapies: Analysis of 122 Cases

Roberto Perez-Alvarez,* Marta Perez-de-Lis,* Candido Diaz-Lagares,†
Jose M. Pego-Reigosa,‡ Soledad Retamozo,† Albert Bove,†
Pilar Brito-Zeron,† Xavier Bosch,§ and Manuel Ramos-Casals, MD, PhD†

Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, et al.

Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases

Semin Arthritis Rheum. 2011;41:256-64



Perez-Alvarez R, et al. Semin Arthritis Rheum. 2011;41:256-64

Table 1 Clinical Characteristics of 122 Patients with ILD Associated with Biological Therapies	
Underlying rheumatic diseases	
Rheumatoid arthritis	108
Inflammatory bowel disease	3
Ankylosing spondylitis	3
Psoriatic arthritis/psoriasis	3
Autoimmune diseases	5
Biological agents	
Etanercept	58
Infliximab	56
Adalimumab	3
Rituximab	5
Demographic characteristics ($n = 53$)	
Female/male	40/13
Mean age at diagnosis of ILD (years ± SEM)	60.02 ± 1.89
Previous therapies ($n = 52$)	
Methotrexate	33 (63%)
Azathioprine	5 (10%)
Leflunomide	3 (6%)
Biological agents	5 (10%)
Previous pulmonary diseases ($n = 52$)	
Previous ILD	20 (38%)
Symptoms at ILD presentation ($n = 50$)	
Dyspnea	43 (86%)
Fever	22 (44%)
Cough	19 (38%)
Malaise	3 (6%)
Pleuritic pain	1 (2%)
Hemoptysis	1 (2%)
Histological biopsy ($n = 26$)	
UIP	7
NSIP	6
COP	5
Diffuse alveolar damage	1
LIP	1
Not classified	6
Therapeutic management ($n = 54$)	
Withdrawal of biological agent	53 (98%)
Corticosteroids	45 (84%)
Immunosuppressive agents	8 (15%)
Intravenous immunoglobulins	2 (4%)
Outcomes ($n = 52$)	
Complete resolution	21 (40%)
Improvement/partial resolution	13 (25%)
No resolution	18 (35%)
Death	15 (29%)

Perez-Alvarez R, et al. Semin Arthritis Rheum. 2011;41:256-64

Anti-TNF - Side Effects

Neurologic side effects:

Central Nervous System

- Multiple sclerosis
- Optic neuritis
- Acute transverse myelitis

Peripheral Nervous System

- Guillain-Barre syndrome
- Miller Fisher Syndrome
- Chronic inflammatory apomyelinotic polyneuropathy
- Multiple mononeuritis
- Axonal sensorimotor polyneuropathy
- Multifocal motor polyneuropathy with conductance block

Researcher/Study	Number of patients with neurological manifestations	Anti – TNF – α factor	CNS impairment
Mohan N, et al. (2001)	19	17 etarnecept,2 infliximab	CNS apomyelinosis
Shin, et al. (2006)	15	9 infliximab, 5 etarnecept	GBS
		1 adalimumab	(Gillian bare syndrome)
Simsek, et al. (2007)	15	8 Infliximab 5 etarnecept	Optic neuritis
		2 adalimumab	
Solomon AJ, et al. (2011)	10	8 etarnecept ,2 Infliximab	8 CNS apomyelinosis 2 PNS apomyelinosis
Fromont A, et al. (2008)	3	3 Abadacept	CNS apomyelinosis
Lees, et al. (1999-2007)	6	6 Infliximab	Suspicion of apomyelinosis
Lozeron et al. (2009)	5	2 infliximab1 etarnecept	Apomyelinotic polyneuropathy
		1 adalimumab	
		1 και με τους 3 anti-TNFs	
Theibich A, et al. (2011)	6	Infliximab etarnecept adalimumab	Indications of apomyelinosis
Seror R, et al. (2013)	33	15 infliximab12 Etarnecept	22 CNS apomyelinosis 11 PNS apomyelinosis
		6 Adalimumab	
Al-Shahi Salman R, (2012)	7	???	CNS apomyelinosis
Theibich A, et al. (2008 – 2011)	6	Infliximab Adalimumab Etanercept	4 CNS apomyelinosis
			2 PNS apomyelinosis
Andreadou E, et al. (2013)	4	1 Adalimumab ,3 Etanercept	CNS apomyelinosis
Li SY, et al.	21	Adalimumab Infliximab	8 CNS apomyelinosis
			13 PNS apomyelinosis
Tektonidou MG, et al. (2007)	2	Infliximab	Polyneuropathy

Lin EJ, Reddy S, Shah VV, Wu JJ.

A review of neurologic complications of biologic therapy in plaque psoriasis

Cutis 2018;101:57-60

TABLE 1. Clinical Presentation and Diagnostic Workup of PML Associated With Biologics

Biologic Agent[a]	Incidence of Associated PML	Clinical Presentation	Diagnostic Workup
Efalizumab[b]	3 cases in the absence of confounding factors (ie, HIV/AIDS, concurrent immunosuppressive therapy)[5]	Multifocal process resulting in diverse clinical manifestations: visual field defects, cortical blindness (20%–50% of patients and often the presenting manifestation[6]), motor weakness, gait abnormalities, incoordination, behavioral and cognitive abnormalities, single neurological deficit	MRI[7]; CSF studies: PCR for John Cunningham virus DNA; gold standard: brain biopsy[8]
Rituximab	1 in 25,000 RA patients[9]		
TNF inhibitors (infliximab, adalimumab, etanercept)[10-13]	Unknown		

Abbreviations: PML, progressive multifocal leukoencephalopathy; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

[a]Most reported cases of PML associated with biologic agents were in patients treated for nonpsoriatic diseases and have been confounded by the use of other immunosuppressive therapies or were unconfirmed PML.

[b]Approved for moderate to severe plaque psoriasis in 2003 but withdrawn from the market in 2009.

Lin EJ, et al. Cutis 2018;101:57-60

TABLE 2. Clinical Presentation and Diagnostic Workup of Demyelinating Disorders Associated With Biologics

Disorder	Biologic Agent	Incidence of Associated Demyelinating Disorder	Clinical Presentation	Diagnostic Workup
Optic neuritis: inflammatory demyelinating process of the optic nerve	Etanercept	49% of reported cases secondary to anti–TNF-α therapy (N=123)[17]	Onset over several hours and peaking 1–2 wk after initial presentation; periocular pain; unilateral loss of visual acuity; Uhthoff symptom: exercise/heat-induced deterioration of visual symptoms; Pulfrich phenomenon: misperception of direction of movement of an object; ipsilateral afferent pupillary defect; scotoma; optic disc pallor; loss of color vision	Clinical triad: visual loss, periocular pain, dyschromatopsia[18]; MRI; CSF analysis
	Infliximab	43% reported cases secondary to anti–TNF-α therapy (N=123)[17]		
	Adalimumab	7% reported cases secondary to anti–TNF-α therapy (N=123)[17]		
Multiple sclerosis: autoimmune inflammatory demyelinating disorder of the central nervous system	Etanercept	51% of reported cases secondary to anti–TNF-α therapy (N=55)[17]	Polysymptomatic onset occurring at 15–50 y of age; presenting symptoms include sensory disturbance (paresthesia and alterations in touch; pin-prick, vibration, facial, position, and postural sensations), weakness in the legs (more common) and arms, and visual disturbance[19]; ataxia; bladder problems; fatigue; Lhermitte sign; Uhthoff symptom (exacerbated by heat); optic neuritis and internuclear ophthalmoplegia	Definitive diagnosis: ≥2 symptomatic attacks (lasting >24 h, separated by at least 1 mo), with at least 1 attack confirmed by objective findings on either neurologic examination, visual evoked potential/response, or MRI; CSF studies
	Adalimumab	27% of reported cases secondary to anti–TNF-α therapy (N=55)[17]		
	Infliximab	20% reported cases secondary to anti–TNF-α therapy (N=55)[17]		

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Table 2. (continued)

Disorder	Biologic Agent	Incidence of Associated Demyelinating Disorder	Clinical Presentation	Diagnostic Workup
Transverse myelitis: immune-mediated spinal cord disorder with neurologic signs of motor, sensory, and autonomic spinal cord dysfunction	Etanercept[20]	Unknown	Associated with systemic autoimmune diseases (ie, RA, scleroderma, SLE); sensory: well-defined (cervical or thoracic) sensory level, below which pain and temperature sensation is altered; motor: initial limb flaccidity followed by hyperreflexia and Babinksi sign; autonomic: bowel and bladder incontinence, urinary urgency or retention, constipation, sexual dysfunction[22]	Clinical presentation, spinal MRI, CSF studies
Guillain-Barré syndrome: acute immune-mediated polyneuropathy characterized by rapidly progressive limb weakness and diminished or absent reflexes	Efalizumab[23]	Unknown	Two-thirds of cases have preceding respiratory or gastrointestinal tract symptoms ~3 wk before presentation[24]; symmetric, rapidly progressive, ascending bilateral weakness of the arms and legs with hyporeflexia or areflexia; limb numbness and pain; facial, respiratory, and bulbar muscle weakness; urinary retention and ileus	Clinical presentation, CSF studies, neurophysiology studies
	Adalimumab,[25,26] infliximab,[27] etanercept[27]	23 cases (adalimumab, n=7; infliximab, n=11; etanercept, n=5) of cases reported in literature to be associated with anti–TNF-α therapy[28]		

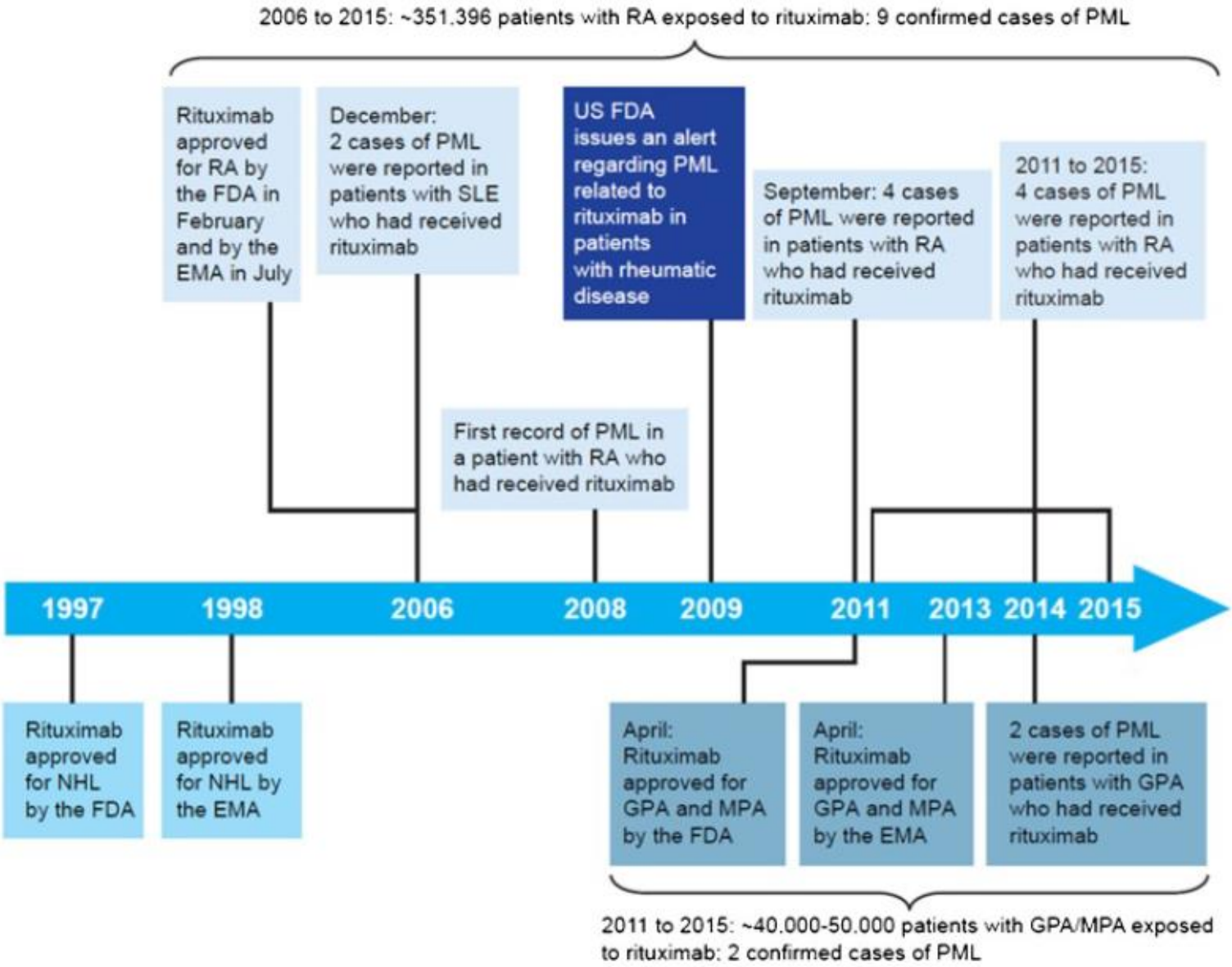
Abbreviations: TNF, tumor necrosis factor; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Lin EJ, et al. Cutis 2018;101:57-60

Journal of NeuroVirology (2018) 24:323–331
https://doi.org/10.1007/s13365-018-0615-7

Progressive multifocal leukoencephalopathy in rituximab-treated rheumatic diseases: a rare event

Joseph R. Berger[1] · Vineeta Malik[2] · Stuart Lacey[3] · Paul Brunetta[4] · Patricia B. Lehane[3]



Berger JR, et al. J Neurovirol. 2018;24:323-331

Table 1 Cases of confirmed PML in patients with RA

Characteristic	Case 1 (Fleischmann 2009)	Case 2 (Clifford et al. 2011)	Case 3 (Clifford et al. 2011)	Case 4 (Clifford et al. 2011)	Case 5 (Clifford et al. 2011)	Case 6	Case 7	Case 8	Case 9
Age, years	50	72	72	62	71	56	58	60	83
Sex	F	F	F	F	F	F	M	F	F
Country	USA	USA	USA	Australia	Sweden	USA	Netherlands	USA	Germany
Date PML confirmed	May 2008	Nov. 2008	Sept. 2009	Oct. 2009	Nov. 2009	March 2010	Not specified	Aug. 2012	Nov. 2014
Duration of RA, years	14	30	3	20	3	6	11	5	7
Relevant medical history	Radiation, Sjögren syndrome with lymphopenia, undetectable complement and CD4, lymphadenopathy	Sjögren syndrome	Sjögren syndrome	Leukopenia	Lymphopenia at baseline, secondary Sjögren syndrome, radiation	None reported	SLE, ANA and anti-DNA antibodies positive, opportunistic infections	SLE	None reported
History of malignancy	Yes	No	No	No	Yes	No	No	No	No
Prior nonbiologics[a, b]	MTX, steroids, HCQ, etodolac	MTX, steroids	Steroids, leflunomide, HCQ	Leflunomide, sulfasalazine, gold, HCQ, steroids	MTX, steroids	Leflunomide MTX	MTX, steroids, sulfasalazine, HCQ	Azathioprine, MTX, CYC, HCQ	MTX, Steroids
Prior biologics[a]	Infliximab	Adalimumab, etanercept	None	Adalimumab, etanercept, anakinra	None	Adalimumab, etanercept	Etanercept, infliximab	None	Denosumab
Concomitant drug[a, b]	MTX, steroids	MTX, steroids	Steroids, leflunomide, HCQ	MTX	HCQ, steroids	MTX, steroids, leflunomide	MTX, steroids	Steroids, MMF	MTX, steroids
Rituximab treatment, no. of courses[b]	4	5	1	≥4	2	3	4	9	unspecified
Latency distribution (time from first rituximab infusion to PML diagnosis)	5 years from first dose and 18 months from last dose	≥26 months after first dose and ≥2 months from last dose	≥7 months	≥18 months from first dose and ≥3 months from last dose	≥15 months from first dose. Not specified relative to last dose	≥23 months from first dose and ≥6 months from last dose	≥28 months from first dose and ≥2 months from last dose	≥56 months from first rituximab dose and ≥6 months from last rituximab dose	≥57 months from first rituximab dose and ≥8 months from last rituximab dose
PML treatment	None reported	Mefloquine	Mefloquine	Mirtazapine and mefloquine	Mirtazapine and mefloquine	Plasmapheresis and mefloquine	Mirtazapine and nitrofurantoin	None reported	None reported
Outcome	Fatal	Fatal	Fatal	Recovering	Recovering	Unknown	Fatal	Fatal	Fatal

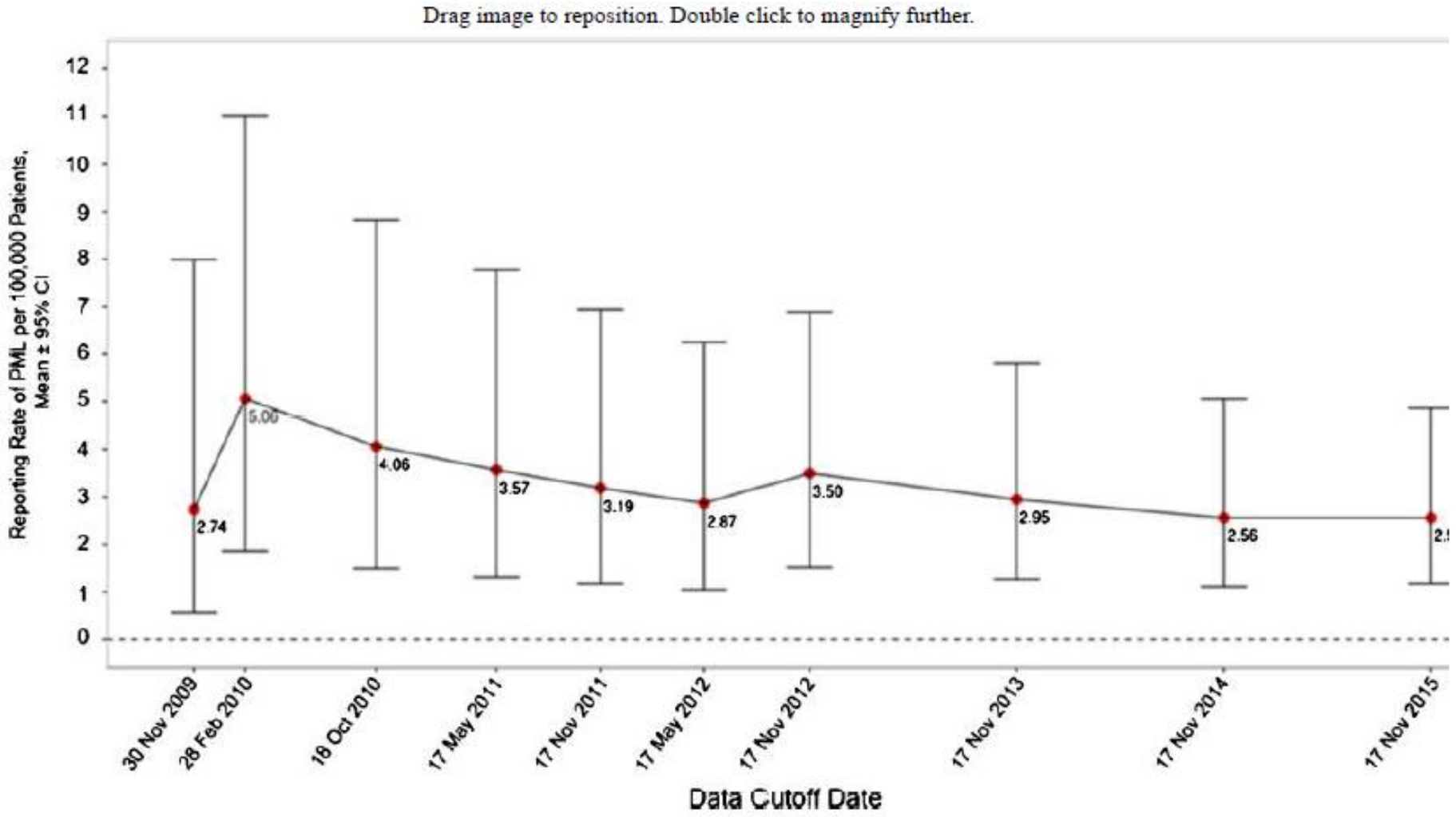
Berger JR, et al. J Neurovirol. 2018;24:323-331

Table 2

Cases of confirmed PML in patients with GPA

Characteristic	Case 1	Case 2
Age, years	70	62
Sex	F	M
Country	Germany	Denmark
Date PML confirmed	July 2012	Sept. 2013
Duration of GPA, years	Not specified	8
Relevant medical history	Immunoglobulin deficiency, breast cancer, diabetes mellitus, arterial hypertension, and chronic stage III renal insufficiency	None reported
Prior treatments	CYC, epirubicin, 5-FU, prednisolone, and MTX	CYC, azathioprine, and high-dose glucocorticoids
Concomitant drug	Azathioprine	None reported
Rituximab treatment	Aug. 2011–March 2012 for GPA; no. of courses not specified	2011–Mar 2013 occasionally as needed for GPA; no. of courses not specified
Latency distribution (time from first rituximab infusion to PML diagnosis)	≈ 11 months from first dose and ≈ 4 months from last dose, symptoms prior to the start of rituximab	≈ 2 years from first dose and ≈ 6 months from the last dose
PML treatment	Immune apheresis to eliminate residual rituximab, cidofovir, mefloquine, and mirtazapine	Mefloquine, mirtazapine, and cytarabine
Outcome	≈ 1 year after PML diagnosis, the patient's condition had improved; however, she continued to experience cognitive deficits and JCV was still detected in her CSF	≈ 3 months after PML diagnosis, the patient's condition had improved

Berger JR, et al. J Neurovirol. 2018;24:323-331



Berger JR, et al. J Neurovirol. 2018;24:323-331

Paradoxical inflammation

Is an intriguing side effect of biologic agents. This inflammation secondary to TNF inhibitors can present with the same types of clinical manifestations for which these drugs are effectively used, including arthritis, uveitis, psoriasis, colitis

- Unmasking subclinical manifestation
- True phenomenon

Paradoxical inflammation

- The most common paradoxical phenomenon is psoriatic skin lesions in pts with RA, SpA and IBD treated with anti TNFs
- Its prevalence varies from 1,6-10% in IBD and 0,6% to 5,3% in RA patients
- The most common sites involvement are the palmoplantar regions and the scalp. Other sites are infrequently involved

Skin lesions after anti-TNF inhibitors

- Psoriatic skin lesions
- Eczema
- Xerosis cutis
- Granuloma annulare
- Pustular folliculitis
- Erythema multiform
- Hidradenitis and sweets syndrome

Treatment: drug discontinuation, topical or small dose of steroids

Mechanism: cytokine shift of TNF and IFNs similar to those of TNF induced SLE

J Cutan Pathol 2012: 39: 481–492
doi: 10.1111/j.1600-0560.2012.01894.x
John Wiley & Sons. Printed in Singapore

Journal of
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Broad range of adverse cutaneous eruptions in patients on TNF-alpha antagonists

Hawryluk EB, Linskey KR, Duncan LM, Nazarian RM.

Broad range of adverse cutaneous eruptions in patients on TNF-alpha antagonists

J Cutan Pathol. 2012;39:481-92.

Table 1. Summary of TNF-alpha antagonist-associated cutaneous eruptions (present study)

Case	Age/ Sex	Underlying condition	Anti-TNF agent	Therapy duration prior to eruption	Anti-TNF agent-associated eruption	Clinical outcome
1	21F, 24F	Crohn's	Infliximab	(a) 2.75 y; (b) 6.75 y	(a) Pustular folliculitis; (b) Psoriasiform dermatitis	(a) Continued therapy after oral antibiotics; (b) Switched anti-TNF agent and added MTX with improvement
2	53M	Crohn's	Infliximab	7 weeks	Erythema multiforme-like hypersensitivity reaction	Improved with topical steroids and discontinuation of anti-TNF agent
3	38M	Crohn's	Adalimumab	21 mo, not continuous	Neutrophilic eccrine hidradenitis and Sweet's syndrome	Improved with prednisone and discontinuation of anti-TNF agent
4	46F	RA, autoimmune hepatitis	Infliximab	4 mo	Drug-induced lupus-like syndrome	Switched to a different anti-TNF therapy with improvement
5	33F	Crohn's	Infliximab	10 y	Leukocytoclastic vasculitis	Initial improvement then progression on clobetasol, with improvement upon subsequent switch in anti-TNF-alpha agent
6	58F	RA	Etanercept	4 mo	Palmoplantar pustular psoriasis	Improved with topical steroids and narrow band ultraviolet-B and discontinuation of anti-TNF agent

Hawryluk EB, et al. J Cutan Pathol. 2012;39:481-92

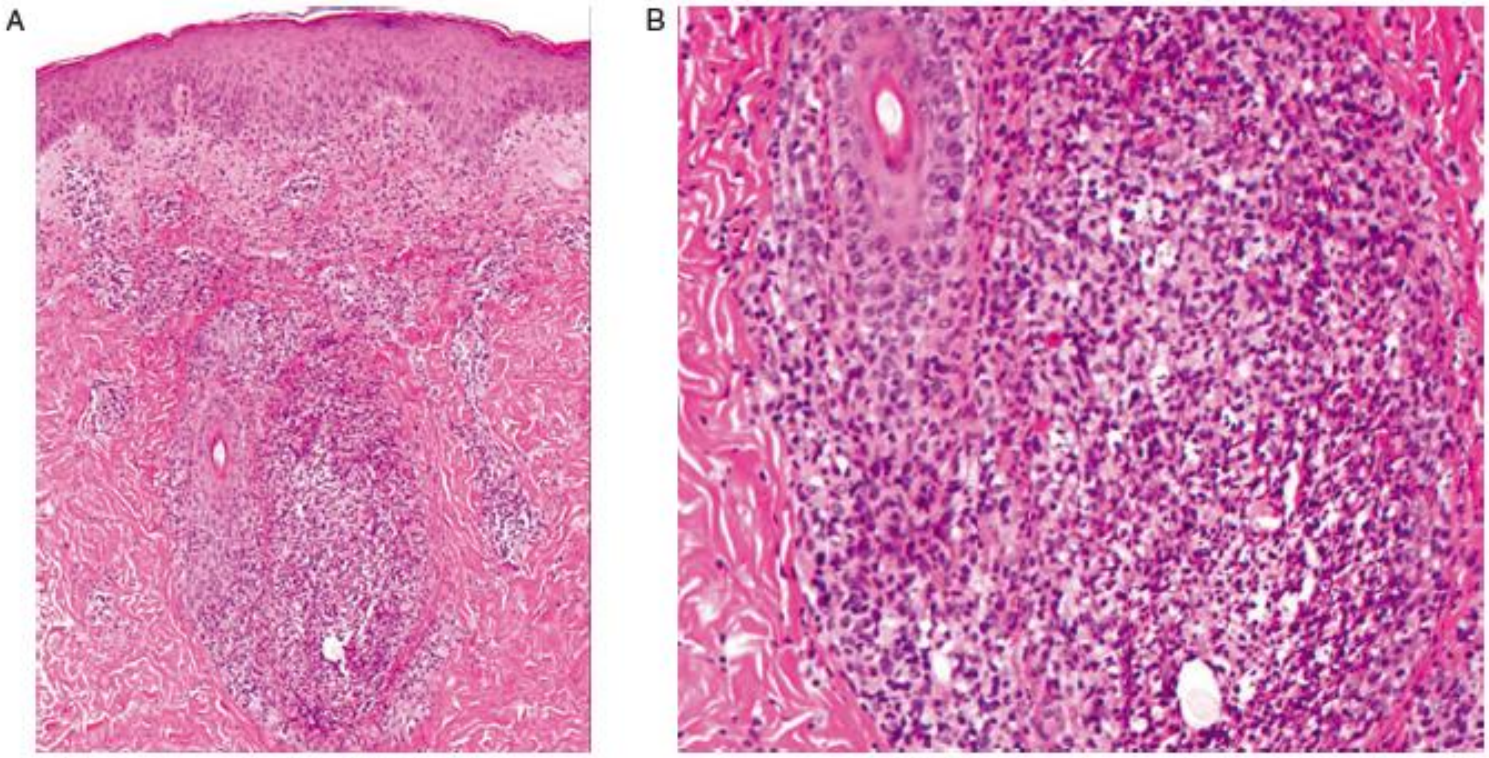


Fig. 1. Case 1: Tumor necrosis factor-alpha antagonist-related acute pustular folliculitis, low-power (panel A, hematoxylin/eosin, ×100) and high-power views (panel B, ×400).

Hawryluk EB, et al. J Cutan Pathol. 2012;39:481-92

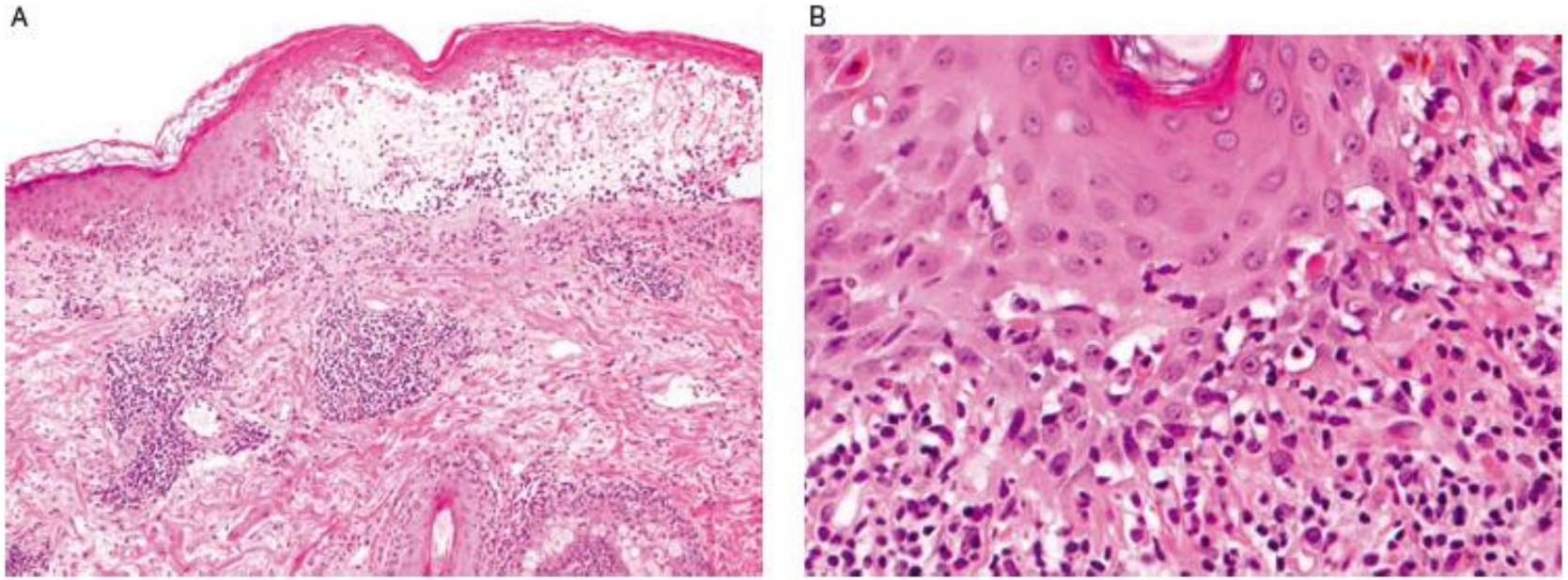


Fig. 2. Case 2: Interface dermatitis with subepidermal blister formation, focal full-thickness epidermal necrosis and perivascular lymphocytic infiltrate consistent with a severe erythema multiforme-like hypersensitivity reaction (panel A, hematoxylin/eosin, ×200). Higher power view reveals interface dermatitis with dyskeratotic keratinocytes within and above the basal layer (panel B, ×400).

Hawryluk EB, et al. J Cutan Pathol. 2012;39:481-92

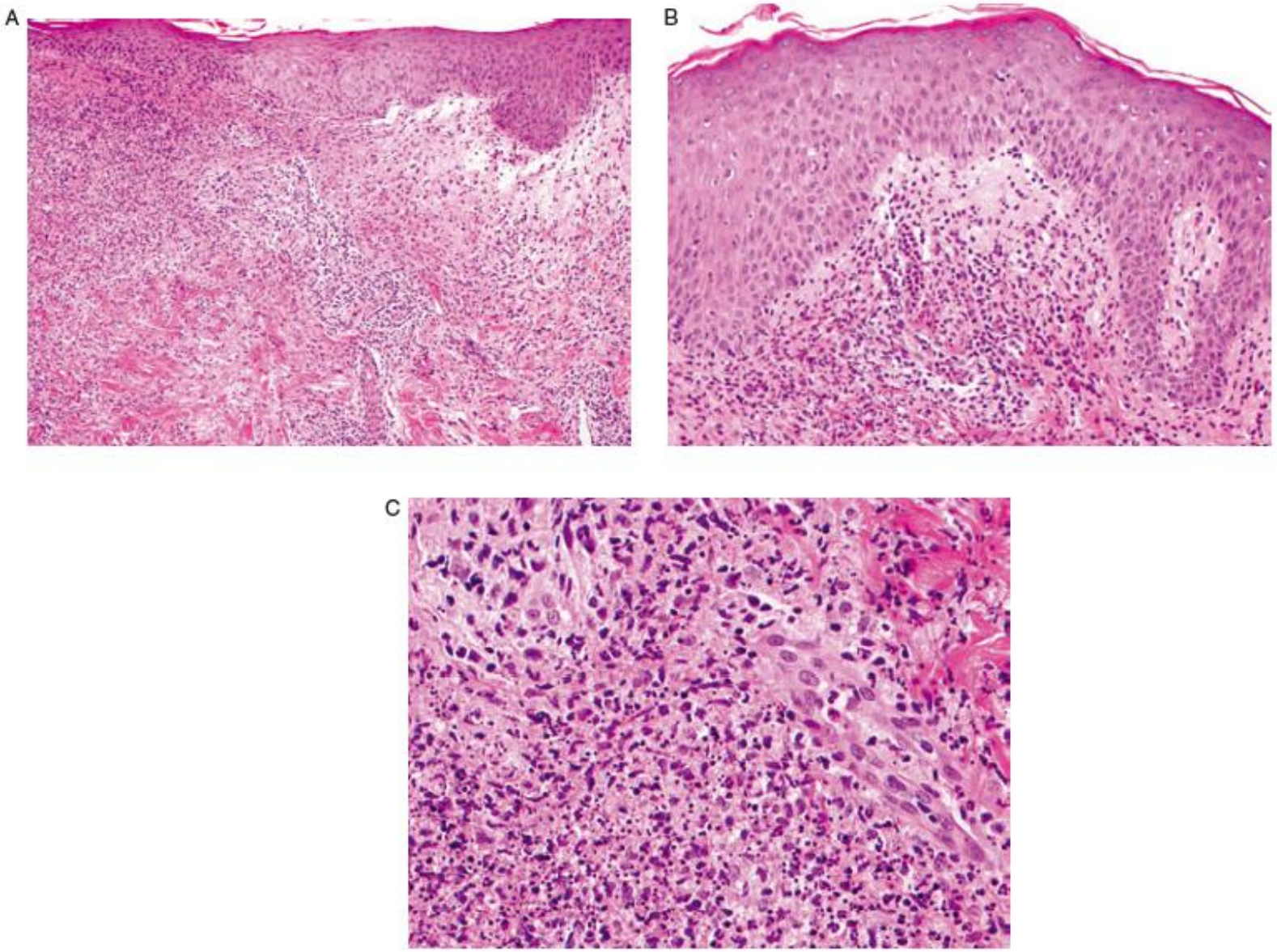


Fig. 3. Case 3: Right shin skin biopsy showing diffuse dermal neutrophilic infiltrate (panel A, hematoxylin/eosin, ×200) and papillary dermal edema (panel B, ×400), with leukocytoclasia and absence of acute vasculitis (panel C, ×400) consistent with drug-induced Sweet's syndrome.

Hawryluk EB, et al. J Cutan Pathol. 2012;39:481-92

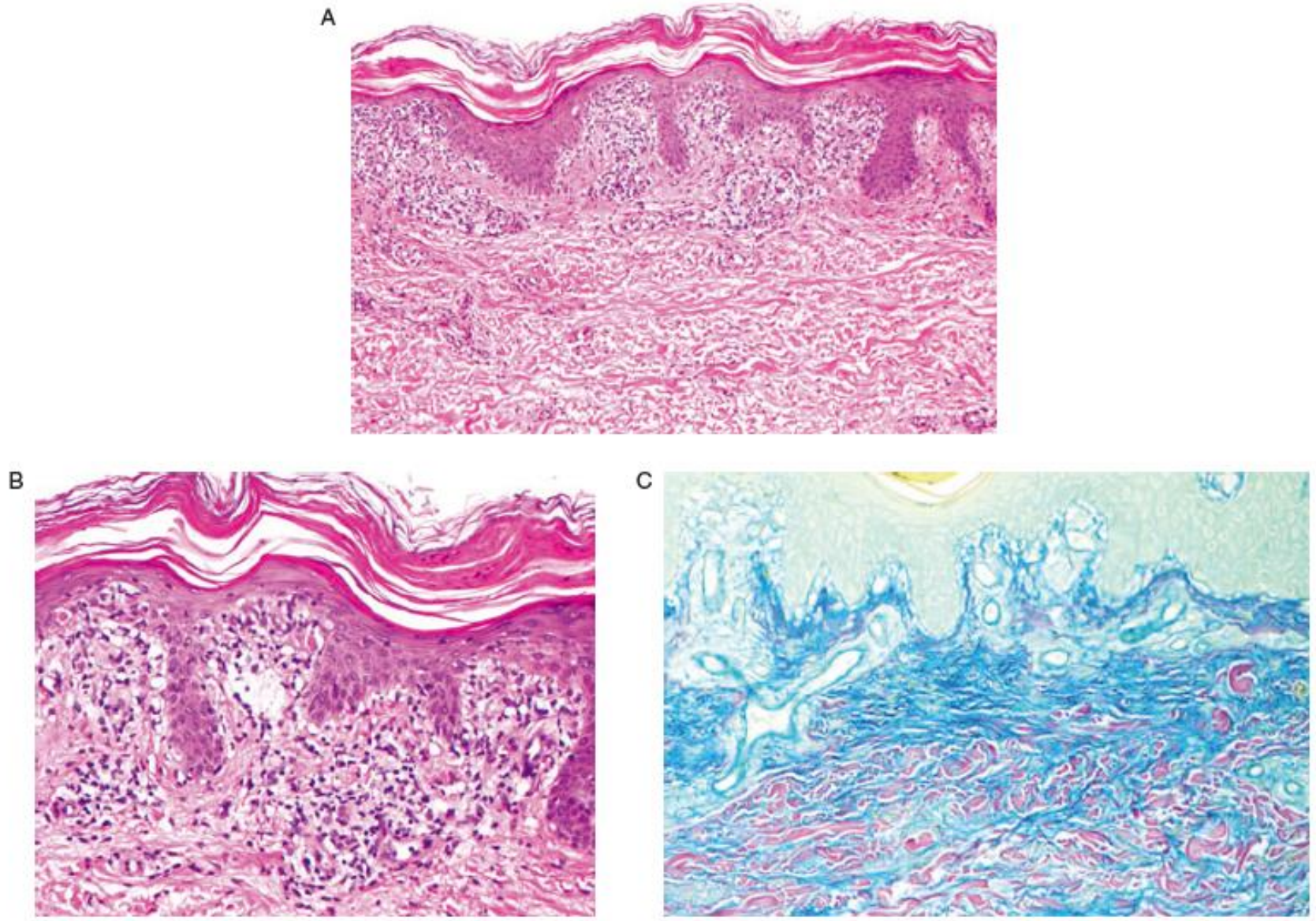


Fig. 4. Case 4: Vacuolar interface dermatitis with dyskeratotic keratinocytes, perivascular lymphocytic infiltrate, medium-power (panel A, hematoxylin/eosin, ×200) and high-power (panel B, ×400) views, and increased interstitial mucin deposition (panel C, colloidal iron, ×400) consistent with a lupus-like drug eruption.

Hawryluk EB, et al. J Cutan Pathol. 2012;39:481-92

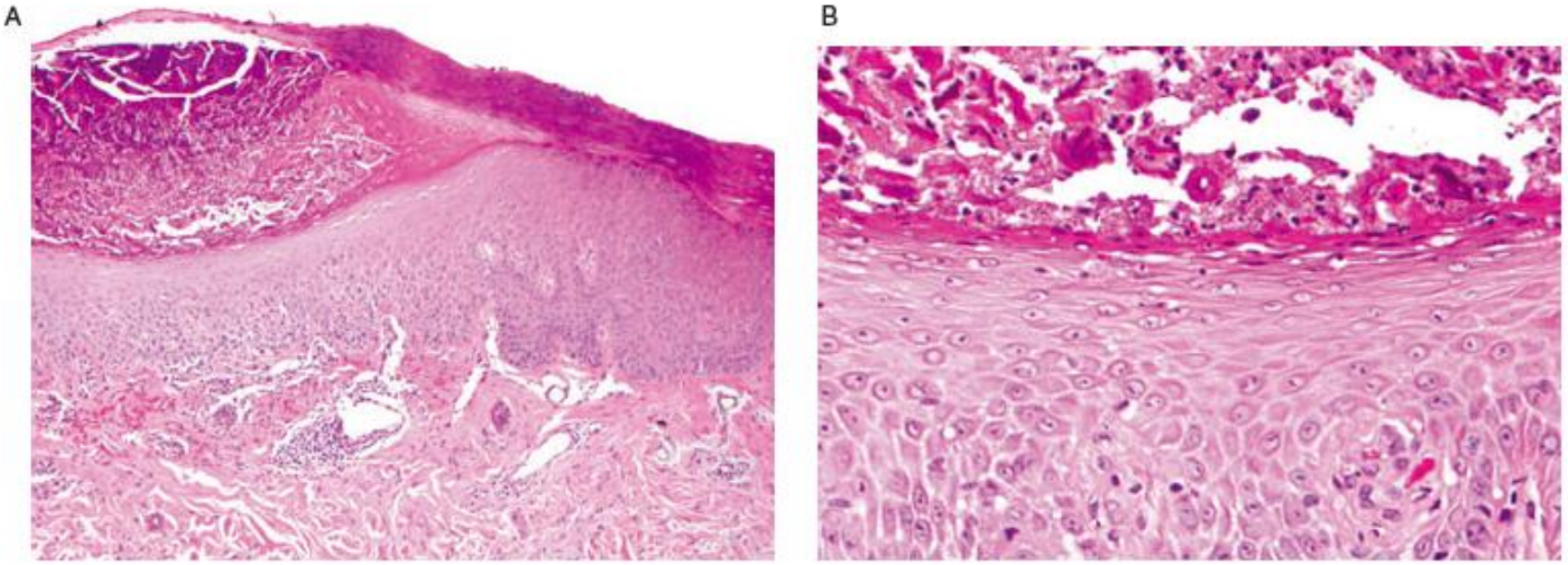


Fig. 6. Case 6: Acral skin with prominent subcorneal microabscess, psoriasiform epidermal hyperplasia (panel A, hematoxylin/eosin, ×200) and diminution of the granular cell layer (panel B, ×400) consistent with palmoplantar pustular psoriasis.

Hawryluk EB, et al. J Cutan Pathol. 2012;39:481-92

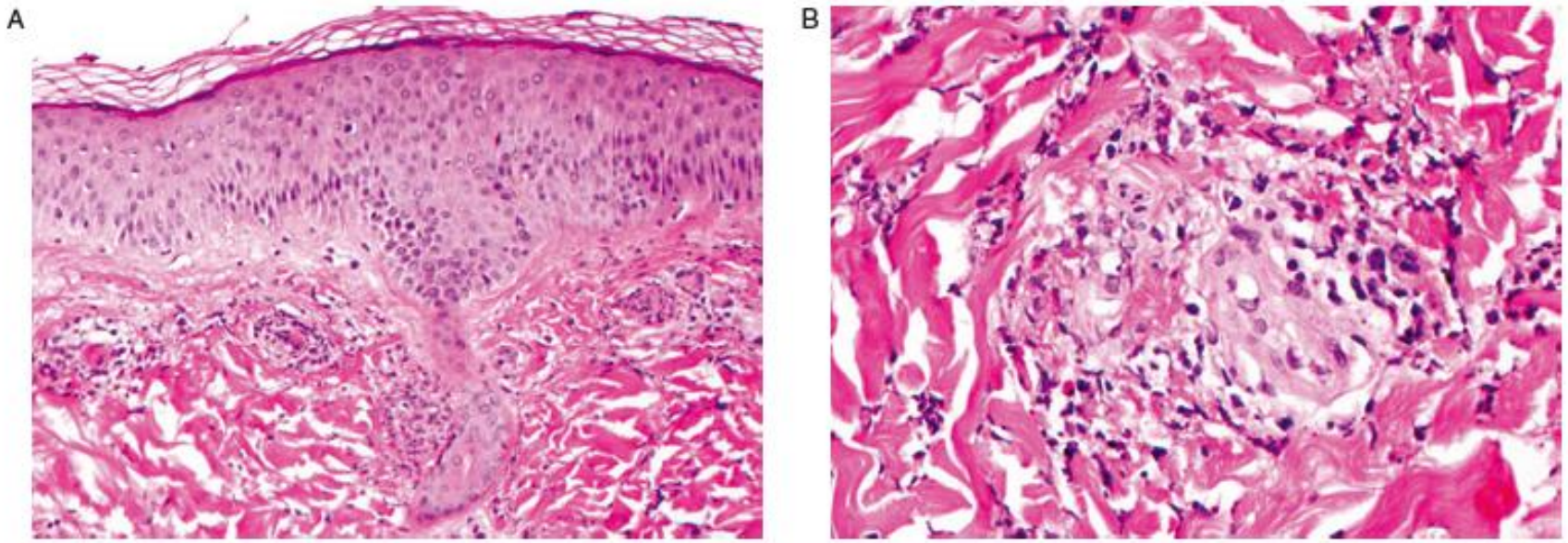


Fig. 5. Case 5: Fibrin deposition (fibrinoid necrosis) of vessel walls with leukocytoclasia (panel A, hematoxylin/eosin, ×200) and admixed eosinophils (panel B, ×400) consistent with drug-induced leukocytoclastic vasculitis.

Hawryluk EB, et al. J Cutan Pathol. 2012;39:481-92

ARTHRITIS & RHEUMATISM
Vol. 52, No. 8, August 2005, pp 2513–2518
DOI 10.1002/art.21233

Psoriasis Induced by Anti–Tumor Necrosis Factor Therapy

A Paradoxical Adverse Reaction

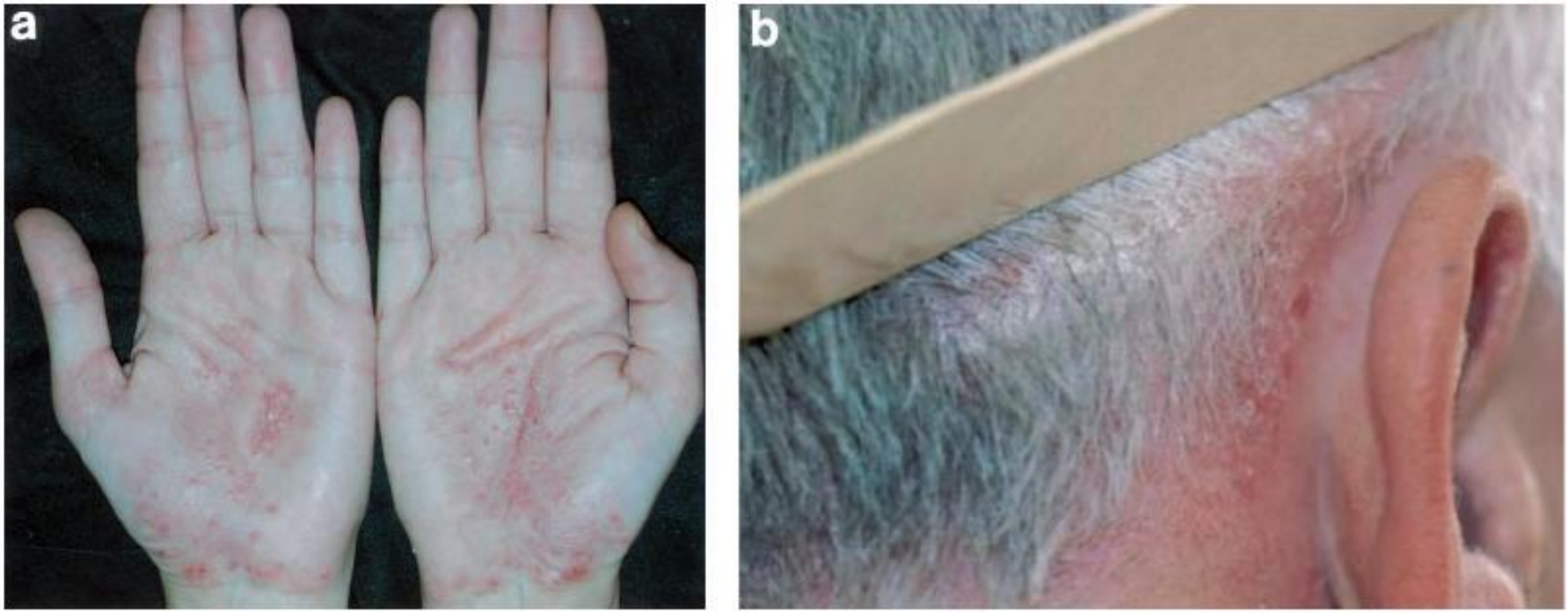
P. P. Sfikakis,[1] A. Iliopoulos,[2] A. Elezoglou,[1] C. Kittas,[1] and A. Stratigos[1]

Table 1. Characteristics of 5 patients in whom psoriasis developed during anti-TNF treatment*

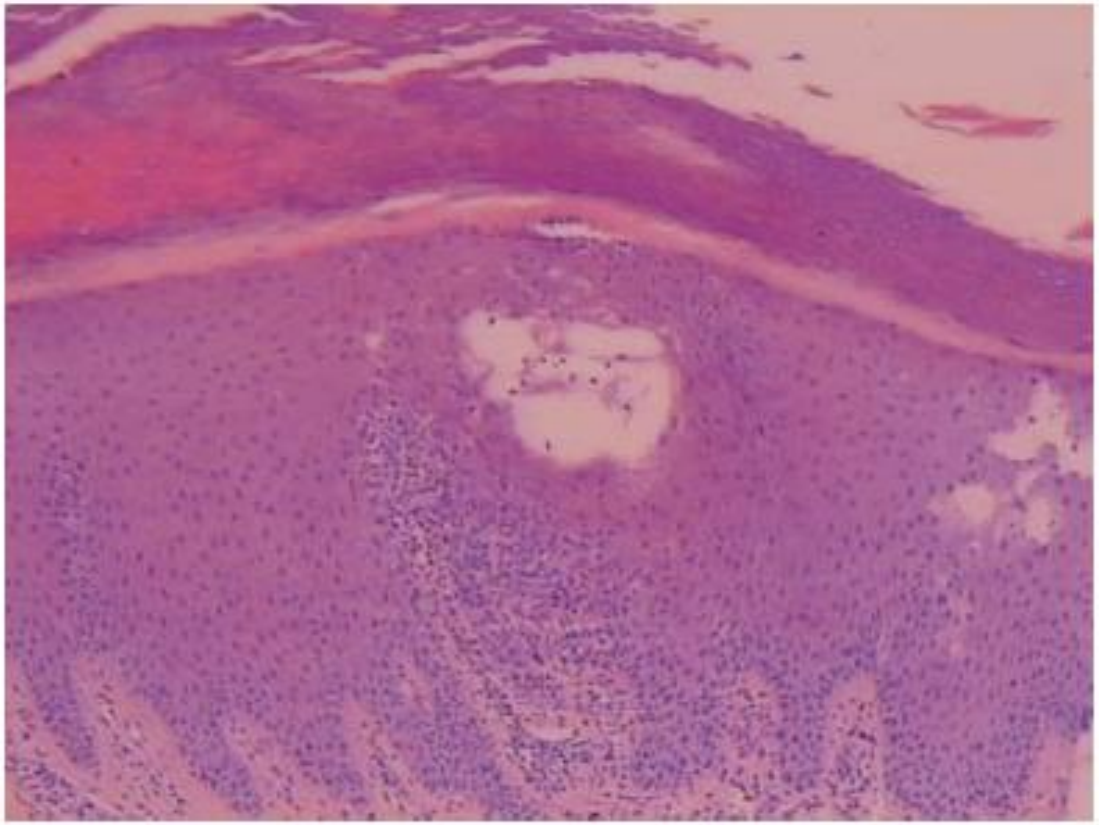
Patient	Age/sex	Diagnosis/ duration, years	Anti-TNF agent	Months after treatment initiation	Concomitant medication	Type of eruption	Nail involvement	Histologic findings
1	33/F	AS/13	INF	9	–	Palmoplantar pustular lesions and scattered erythematous scaly plaques on arms, thighs, lateral trunk	–	Psoriasiform hyperplasia, intraepidermal pustules
2	65/F	RA/21	ADA	9	LEF, SSZ	Palmoplantar pustular lesions, psoriasiform plaques on elbows, arms, thighs	Onycholysis, "oil-spotting" (nail of right thumb)	Intraepidermal pustule, parakeratosis, acanthosis, perivascular infiltrate
3	49/M	ABD/20	INF	6	AZA	Extensive erythematous plaques on the scalp with silvery white scale	–	Parakeratosis, acanthosis, elongation of rete ridges, perivascular inflammatory infiltrate
4	43/M	ABD/21	INF	7	AZA	Palmoplantar pustular lesions, scaly plaques on elbows, knees, scalp	Onycholysis, subungual keratosis in fingernails and toenails	Not done
5	48/F	RA/14	ETA	7	MTX, LEF	Pustules on soles, scaly plaques on elbows, tibia	Subungual hyperkeratosis and onychodystrophy of toenails	Small intraepidermal pustule with neutrophils, psoriasiform hyperplasia, dilated capillaries in dermal papillae

* Anti-TNF = anti–tumor necrosis factor; AS = ankylosing spondylitis; INF = infliximab; RA = rheumatoid arthritis; ADA = adalimumab; LEF = leflunomide; SSZ = sulfasalazine; ABD = Adamantiades-Behçet's disease; AZA = azathioprine; ETA = etanercept; MTX = methotrexate.

Sfikakis PP, et al. Arthritis Rheum 2005;52:2513-8



Sfikakis PP, et al. Arthritis Rheum 2005;52:2513-8



Sfikakis PP, et al. Arthritis Rheum 2005;52:2513-8

Our experience

Granuloma annulare induced by anti-tumour necrosis factor therapy

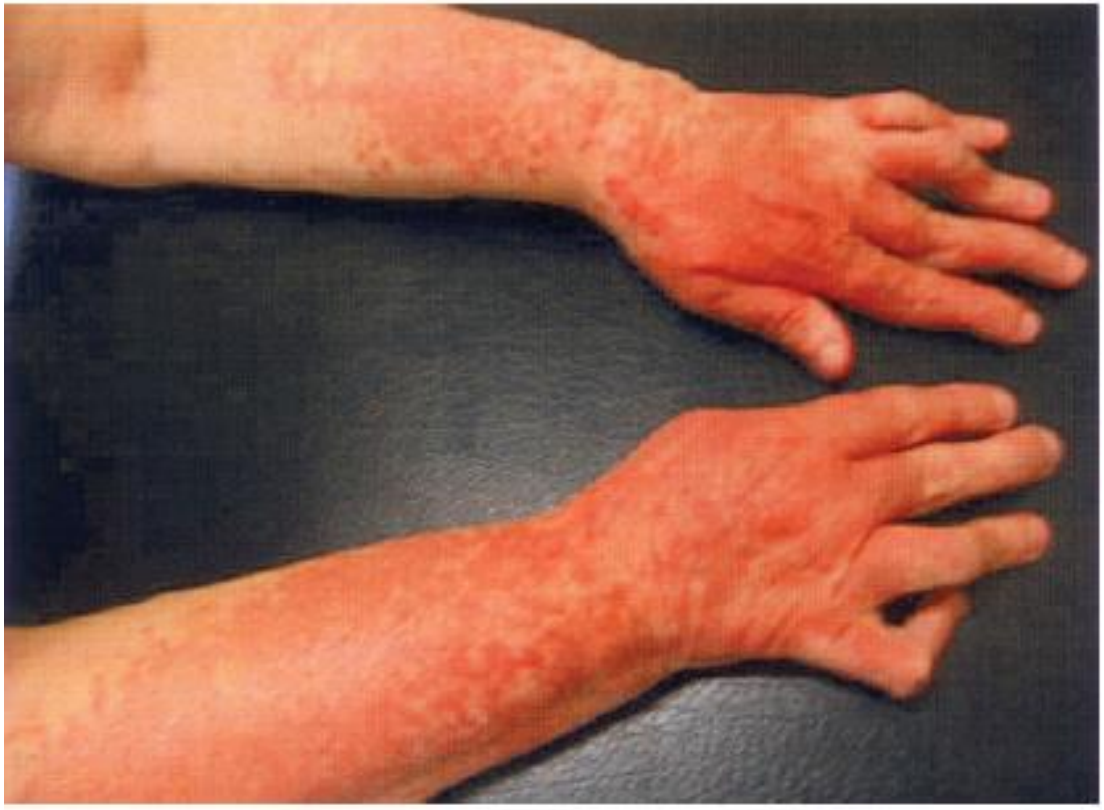
P V Voulgari, T E Markatseli, S A Exarchou, A Zioga and A A Drosos

Ann Rheum Dis 2008;67;567-570; originally published online 29 Aug 2007;
doi:10.1136/ard.2007.075663

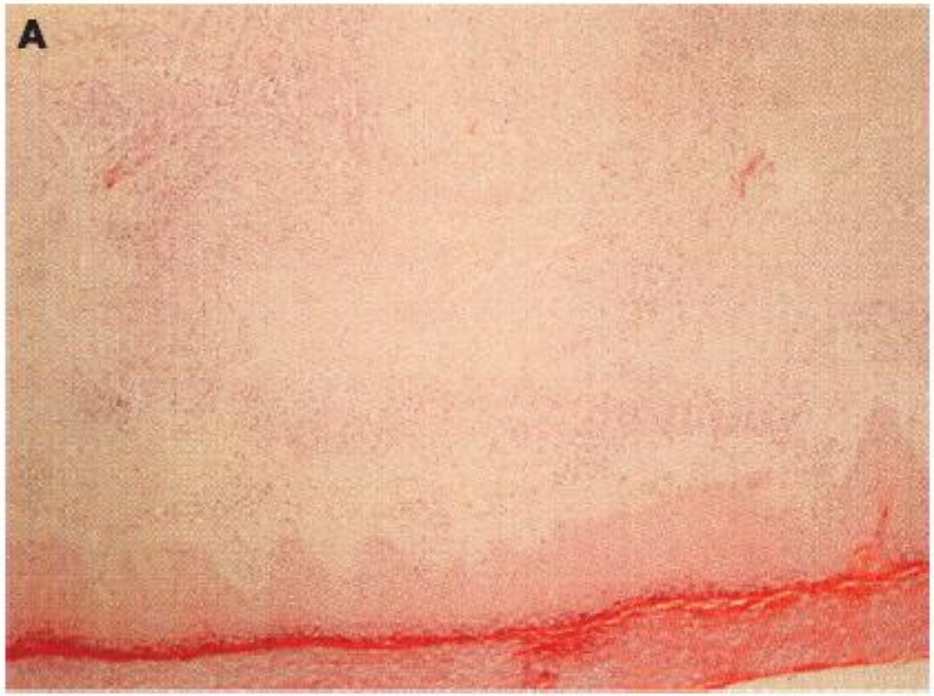
Table 1 Clinical characteristics of nine patients with rheumatoid arthritis who developed granuloma annulare during anti-TNF therapy

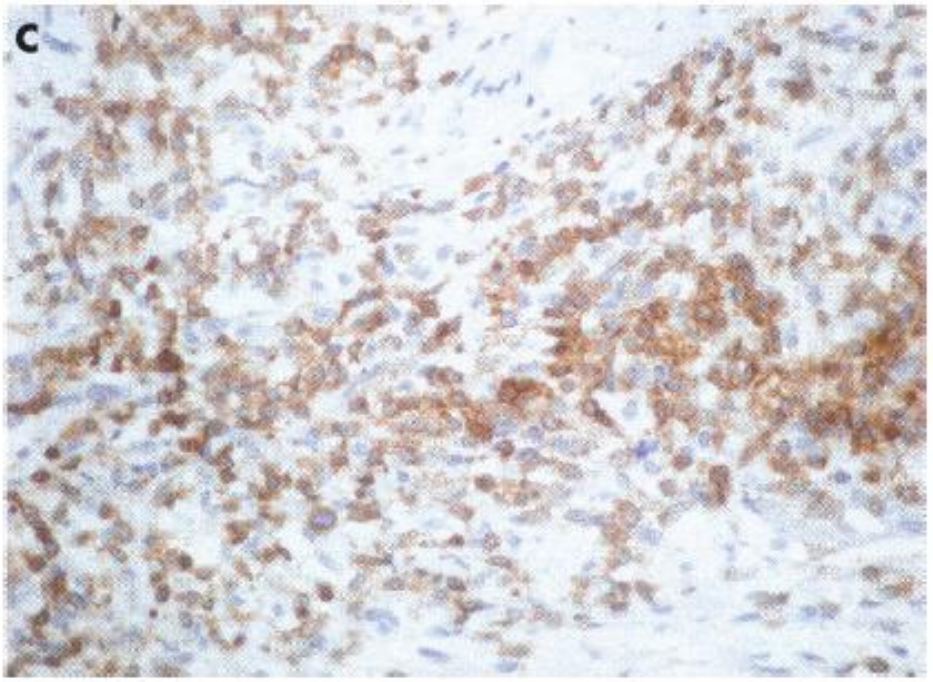
Patients	Age/ sex	Disease duration (years)	Rheumatoid factor	Anti-TNF agent	Time of occurrence (months)	Concomitant treatment	Type of skin lesion	Location	Outcome
1	33/F	16.5	+	Infliximab	9	MTX: 15 mg/week	Generalised	Hands and fingers	Infliximab stopped
						Prednisone: 5 mg/day			Resolution
2	32/M	8.3	–	Infliximab	6	MTX 15 mg/week	Generalised	Forearms	Treatment continued
						CsA: 200 mg/day			Resolution
3	37/F	17.0	+	Adalimumab	14	MTX: 15 mg/week	Generalised	Hands and forearms	Treatment continued
									Resolution
4	76/F	22.0	+	Adalimumab	14	MTX: 15 mg/week	Generalised	Hands and forearms	Treatment continued
									Resolution
5	23/F	4.0	+	Adalimumab	4	MTX: 12.5 mg/week	Generalised	Elbows	Treatment continued
									Resolution
6	44/F	20.5	+	Adalimumab	6	MTX: 12.5 mg/week	Generalised	Fingers and hands	Treatment continued
									Resolution
7	60/F	17.5	+	Adalimumab	3	MTX: 15 mg/week	Generalised	Fingers, hands and forearms	Adalimumab stopped
						LFN: 20 mg/day			Resolution
8	45/F	20.2	+	Adalimumab	6	MTX: 12.5 mg/week	Generalised	Forearms	Treatment continued
						CsA: 150 mg/day			Resolution
9	36/F	4.7	+	Etanercept	8	MTX: 12.5 mg/week	Generalised	Fingers and hands	Treatment continued
						Prednisone: 5 mg/day			Resolution

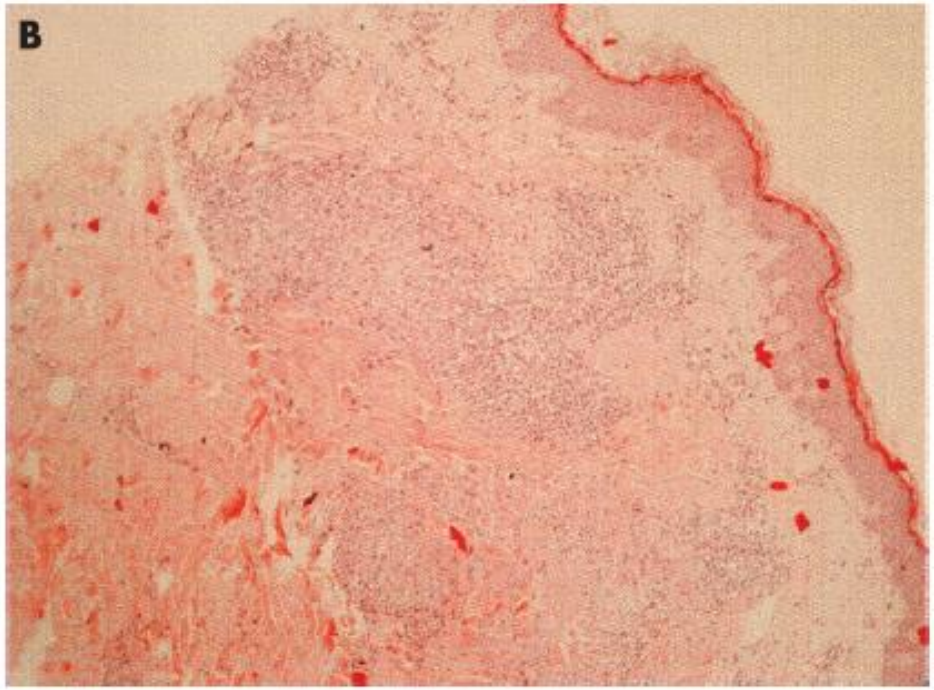
Voulgari PV, et al. Ann Rheum Dis 2008;67:567-70



Voulgari PV, et al. Ann Rheum Dis 2008;67:567-70







Voulgari PV, et al. Ann Rheum Dis 2008;67:567-70.

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Immune-mediated skin lesions in patients treated with anti-tumour necrosis factor alpha inhibitors

SA Exarchou, PV Voulgari, TE Markatseli, A Zioga & AA Drosos

Table 1. Clinical characteristics of patients with RA, AS, or PsA treated with TNFα inhibitors.

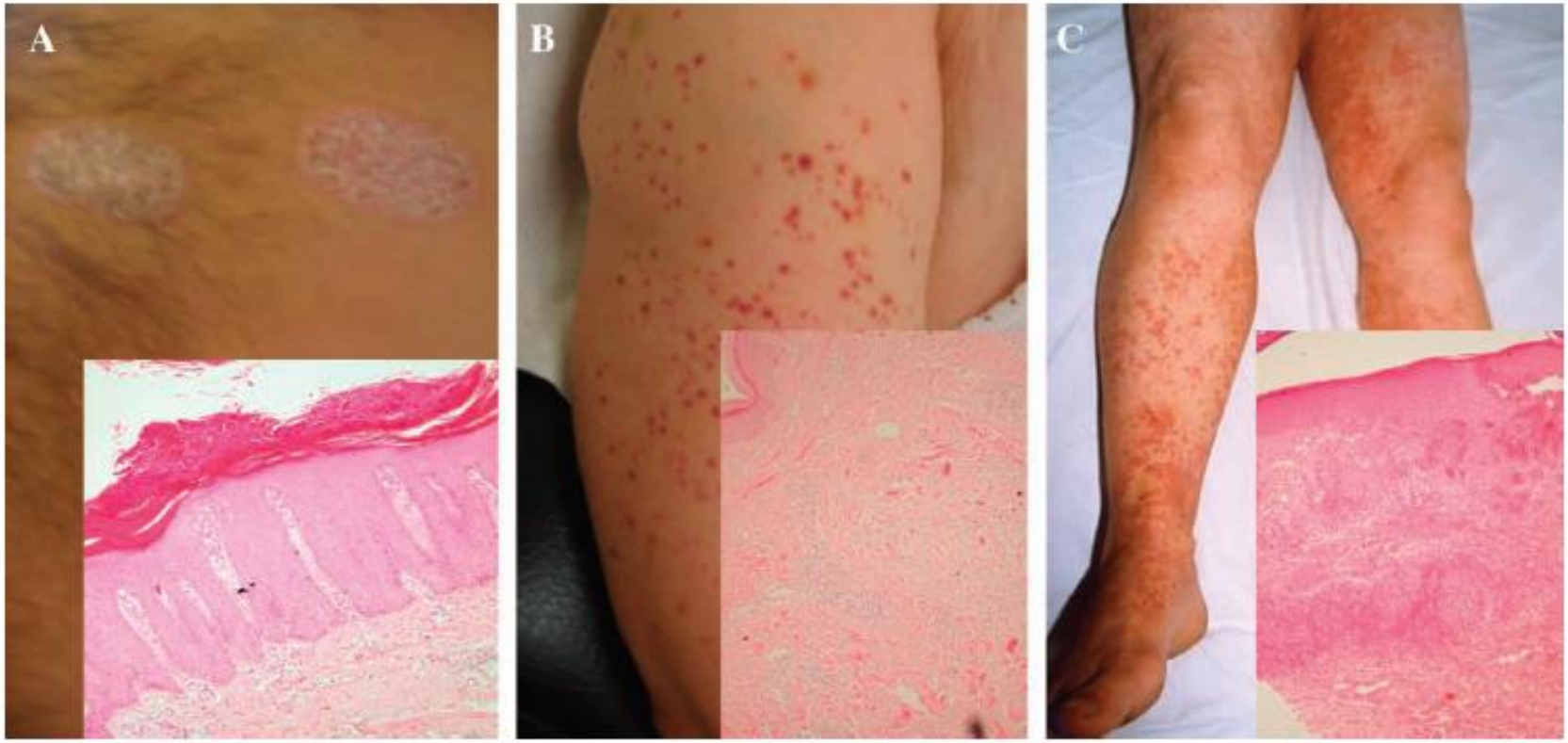
Clinical data	RA	AS	PsA
Number of patients	252	93	90
Female/male	185/67	22/71	46/44
Age (years), mean (SD)	60.5 (10.5)	38.6 (12.5)	48.5 (9.6)
Disease duration (years), mean (SD)	12.8 (5.5)	11.2 (7.6)	10.8 (8.8)
Disease-modifying anti-rheumatic drugs, n (%)	252 (100)	3 (3.2)	72 (80)
Methotrexate	150 (59.5)	1 (1.1)	35 (39)
Leflunomide	51 (20.3)	–	11 (11)
Sulfasalazine	–	2 (2.1)	–
Cyclosporin	51 (20.2)	–	36 (40)
TNFα blockers, n (%)			
Infliximab	146 (58.0)	88 (94.5)	50 (55.5)
Adalimumab	72 (28.5)	3 (3.2)	5 (5.5)
Etanercept	34 (13.5)	2 (2.3)	35 (39)

Exarchou SA, et al. Scand J Rheumatol 2009;38:328-31

Table 2. Characteristics of patients with RA who developed IMSLs.

IMSL development	Infliximab (n = 146)	Adalimumab (n = 72)	Etanercept (n = 34)	Total
Psoriatic-like skin lesions	7	3	1	11
Granuloma annulare	3	6	1	10
Skin vasculitis	2	2	1	5
Alopecia areata	1	1	–	2
Discoid lupus erythematosus	1	–	1	2
Lichen planus	–	1	–	1
Vitiligo	1	–	–	1
Total	15	13	4	32

Exarchou SA, et al. Scand J Rheumatol 2009;38:328-31

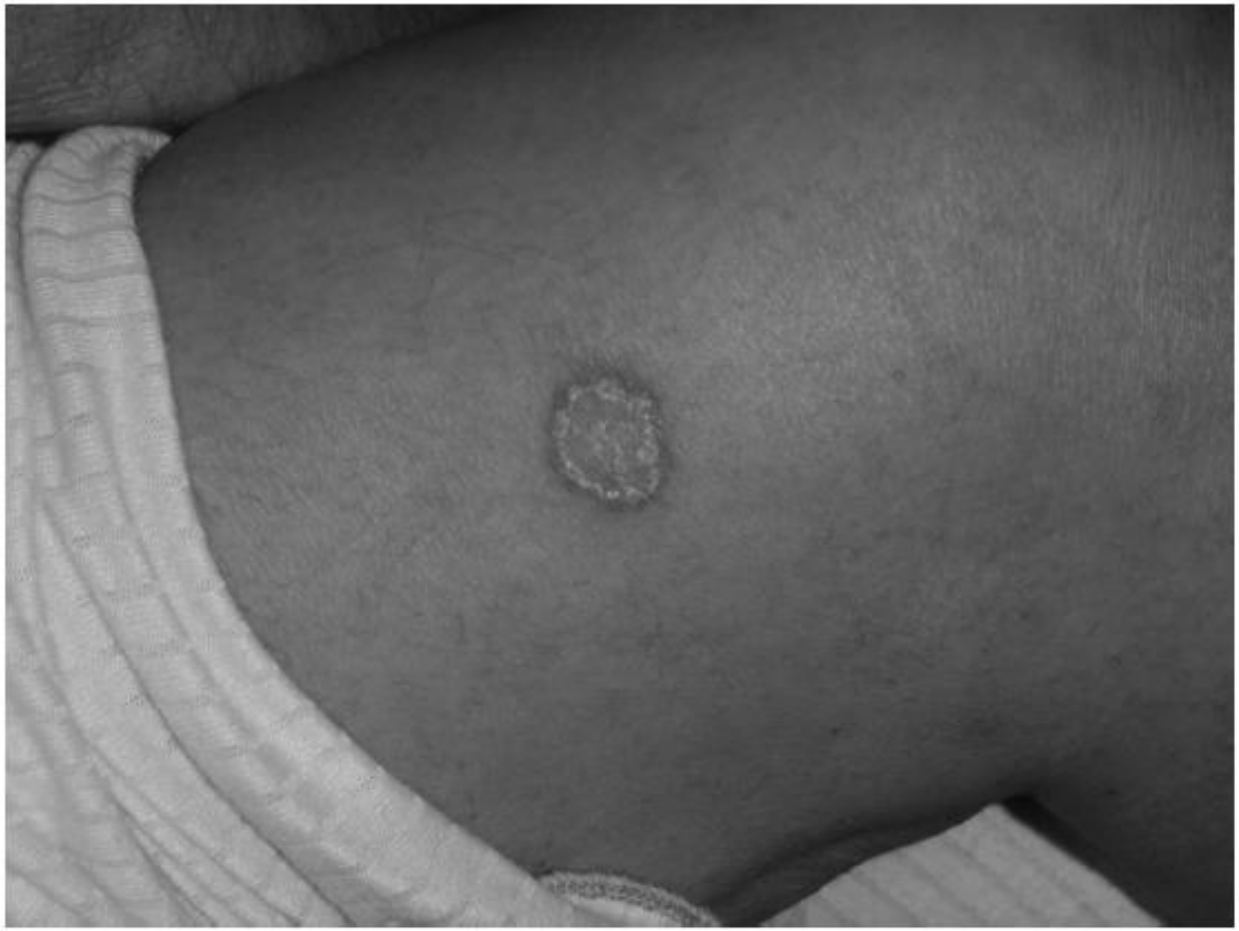


Exarchou SA, et al. Scand J Rheumatol 2009;38:328-31

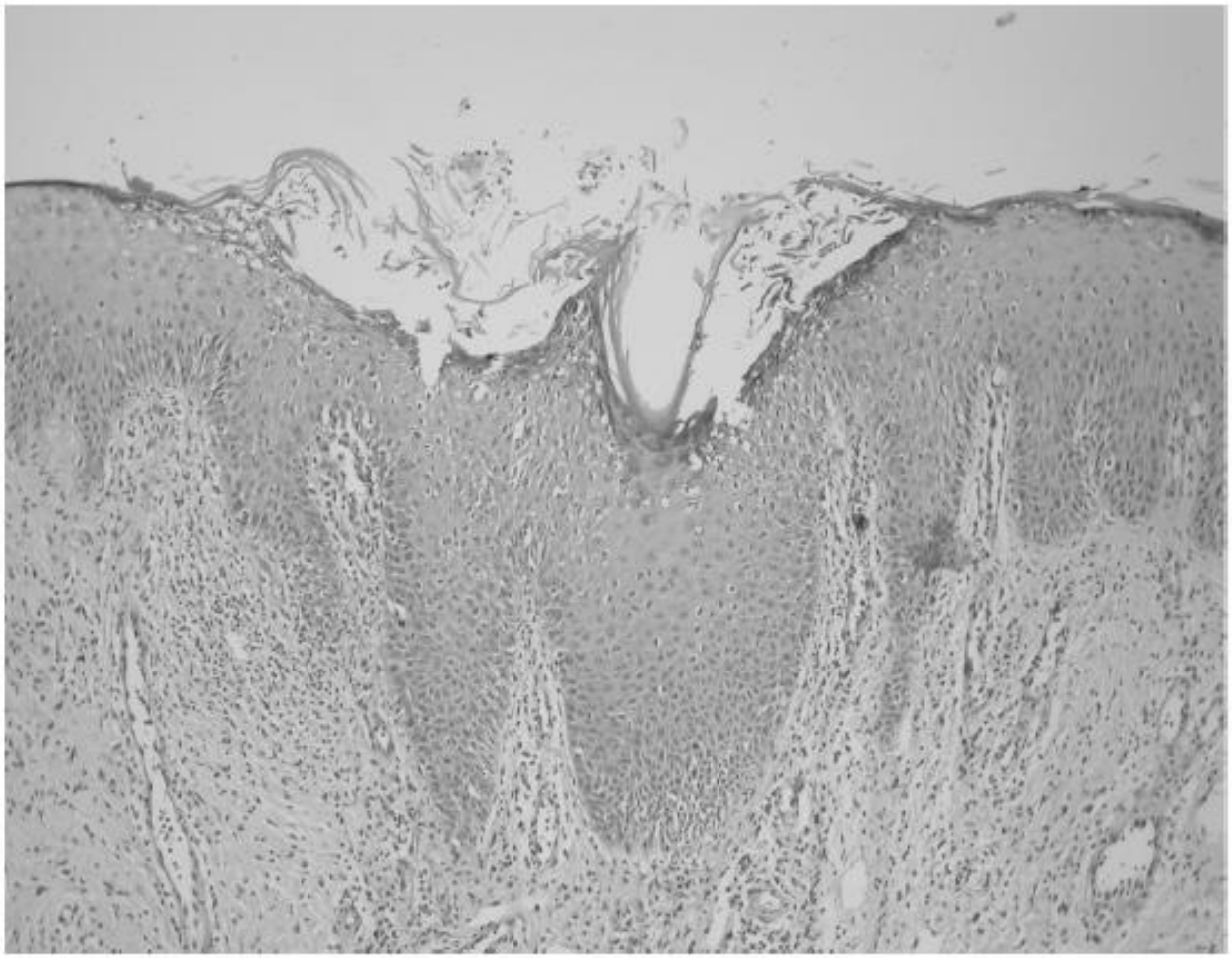
Markatseli TE, Kaltsonoudis ES, Voulgari PV, et al.

Induction of psoriatic skin lesions in a patient with rheumatoid arthritis treated with rituximab

Clin Exp Rheumatol 2009;27:996-8



Markatseli TE, et al. Clin Exp Rheumatol 2009;27:996-8



Markatseli TE, et al. Clin Exp Rheumatol 2009;27:996-8

Rheumatology International (2019) 39:353–357
https://doi.org/10.1007/s00296-018-4212-0

Rheumatology
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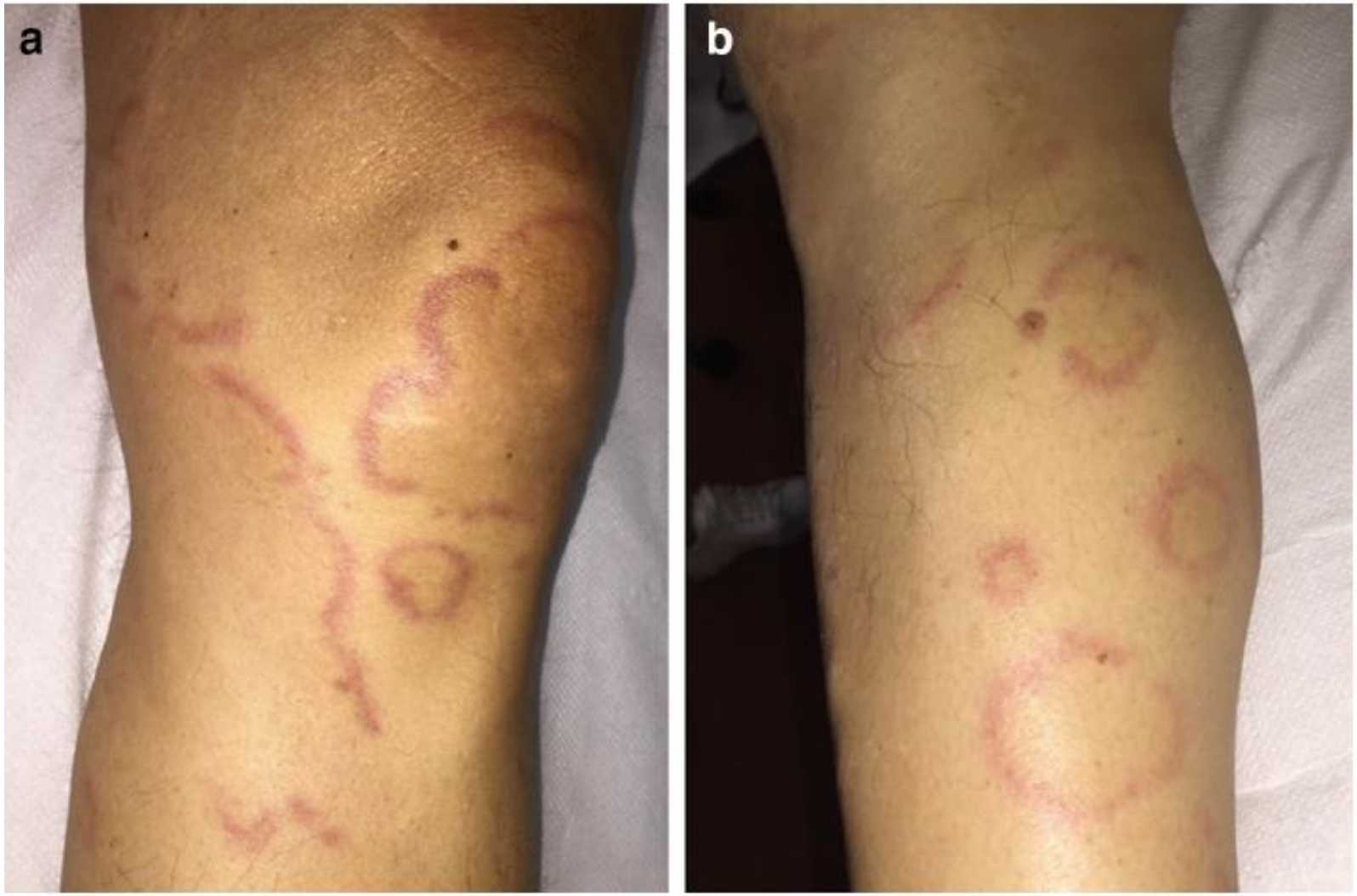
CASES WITH A MESSAGE

Granuloma annulare development in a patient with rheumatoid arthritis treated with tocilizumab: case-based review

Eleftherios Pelechas[1] · Alexandra Papoudou-Bai[2] · Paraskevi V. Voulgari[1] · Alexandros A. Drosos[1]



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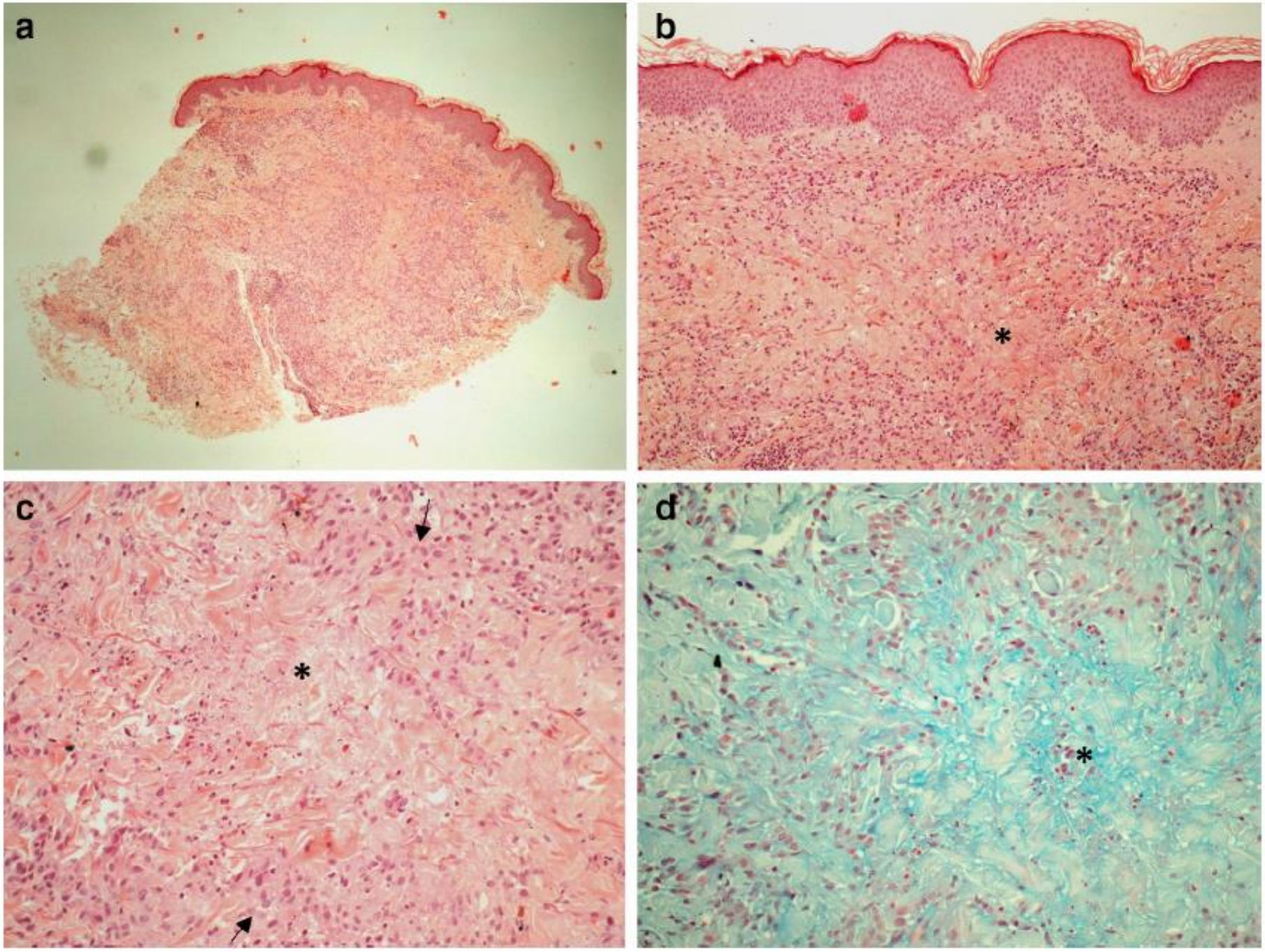

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Table 1 Granuloma annulare after treatment with bDMARDs

Author, year [citation]	Number of cases	Disease treated	bDMARD used	Treatment	Outcome
Devos SA et al. 2003 [11]	1	PsA	INF	Cs	Complete resolution
Voulgari PV et al. 2005 [7]	9	RA	2 INF 6 ADA 1 ETN	Prednisone 10 mg/day plus topical Cs (1 patient on INF and 1 on ADA discontinued treatment)	Complete resolution
Exarchou S. 2008 [3]	1	RA	INF	Prednisone 10–15 mg/day plus topical Cs	Complete resolution
Ratnarathorn M et al. 2011 [12]	1	RA	ADA	Discontinuation of ADA	Complete resolution
			ETN	Discontinuation of ETN	Complete resolution
Bonomo et al. 2017 [14]	1	PsA	Secukinumab	Topical Cs (clobetasol propionate) and discontinuation of secukinumab	Marked improvement (within 8 months)
Clark et al. 2018 [15]	1	Psoriasis	Secukinumab	Triple antibiotic therapy (rifampin, levofloxacin, minocycline)	No improvement
				Etanercept	Complete resolution (within 6 weeks)
Pelechas et al. 2018 [current case]	1	RA	TCZ	Discontinuation of TCZ, Cs	Complete resolution (within 4 weeks)

Pelechas E, et al. Rheumatol Int 2019;39:353–357

Cutaneous autoimmune phenomena of the anti- TNF a biosimilars. Case based review

Pelechas E. , Papoudou- Bai A. , Voulgari P. V., Drosos AA
Current Rheumatology Reviews in press

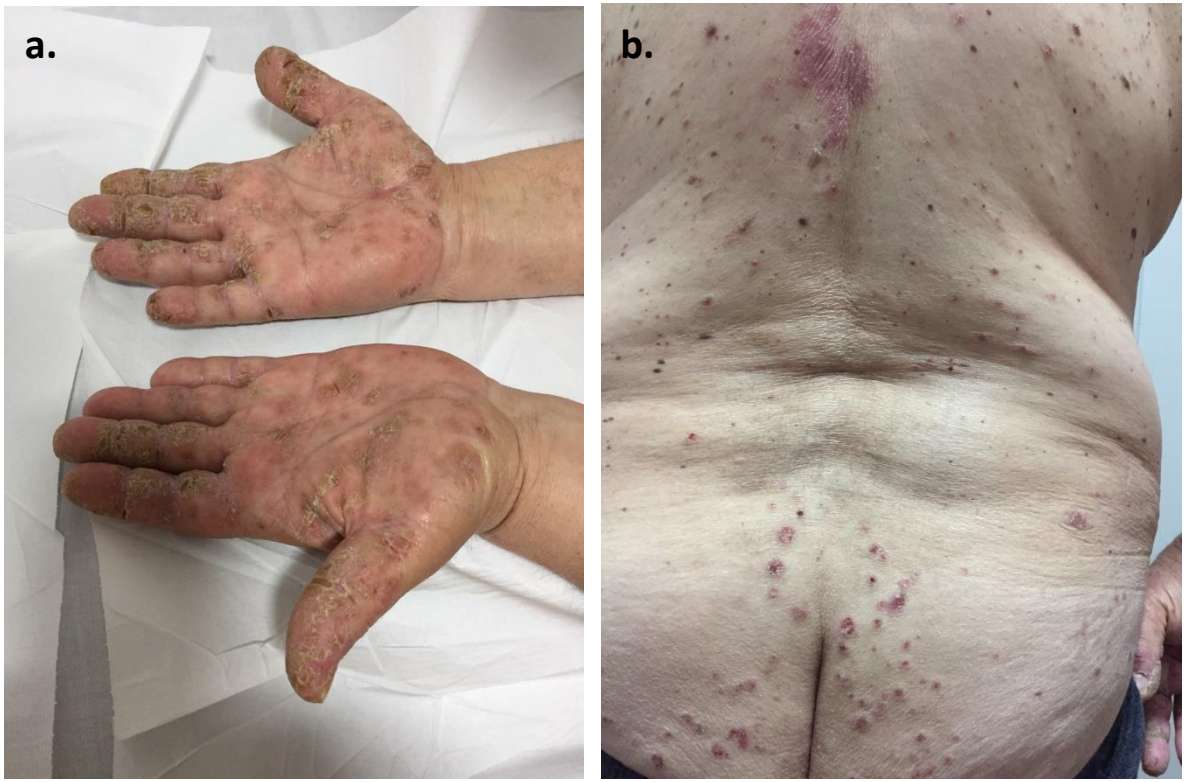

Figure 1 Psoriasiform skin lesions; 1a. Multiple skin lesions on the palmar surface of both hands with a grade 2-3 erythema, scales and induration while on 1b multiple scattered eruptions are evident on the torso (back and gluteal regions).

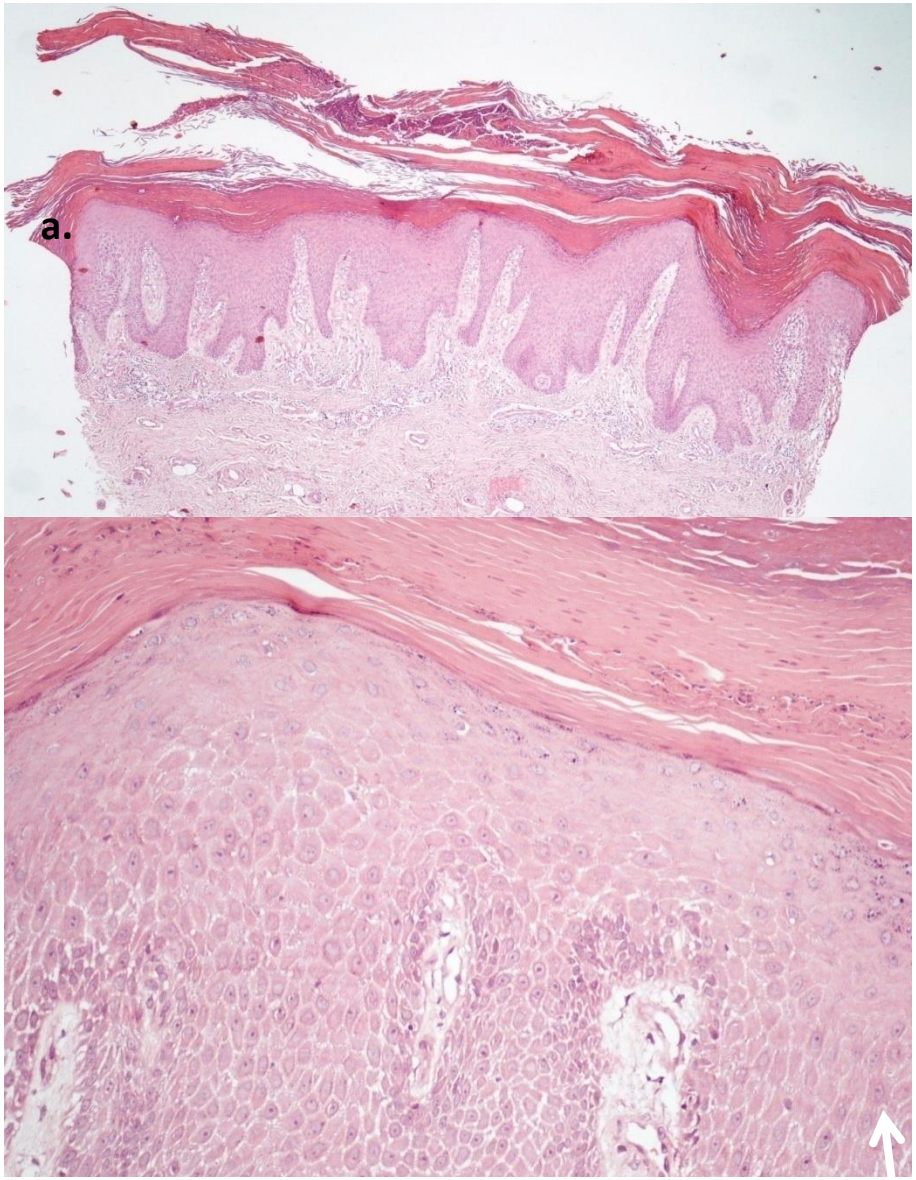

Figure 2 Histological features of psoriasis in dermal biopsy (**2a**): epidermal hyperplasia, parakeratosis, Munro microabcesses, thin granular cell layer, downward elongation of rete ridges and dilated dermal capillaries (hematoxylin-eosin, 40x magnification). At higher magnification (**2b**), Munro microabcess (accumulation of neutrophils in parakeratotic scale – white arrow), thin granular cell layer (black arrow) and prominent dermal capillaries (asterisk) are shown (hematoxylin-eosin, 200x magnification).

TNF-induced lupus. A case-based review.

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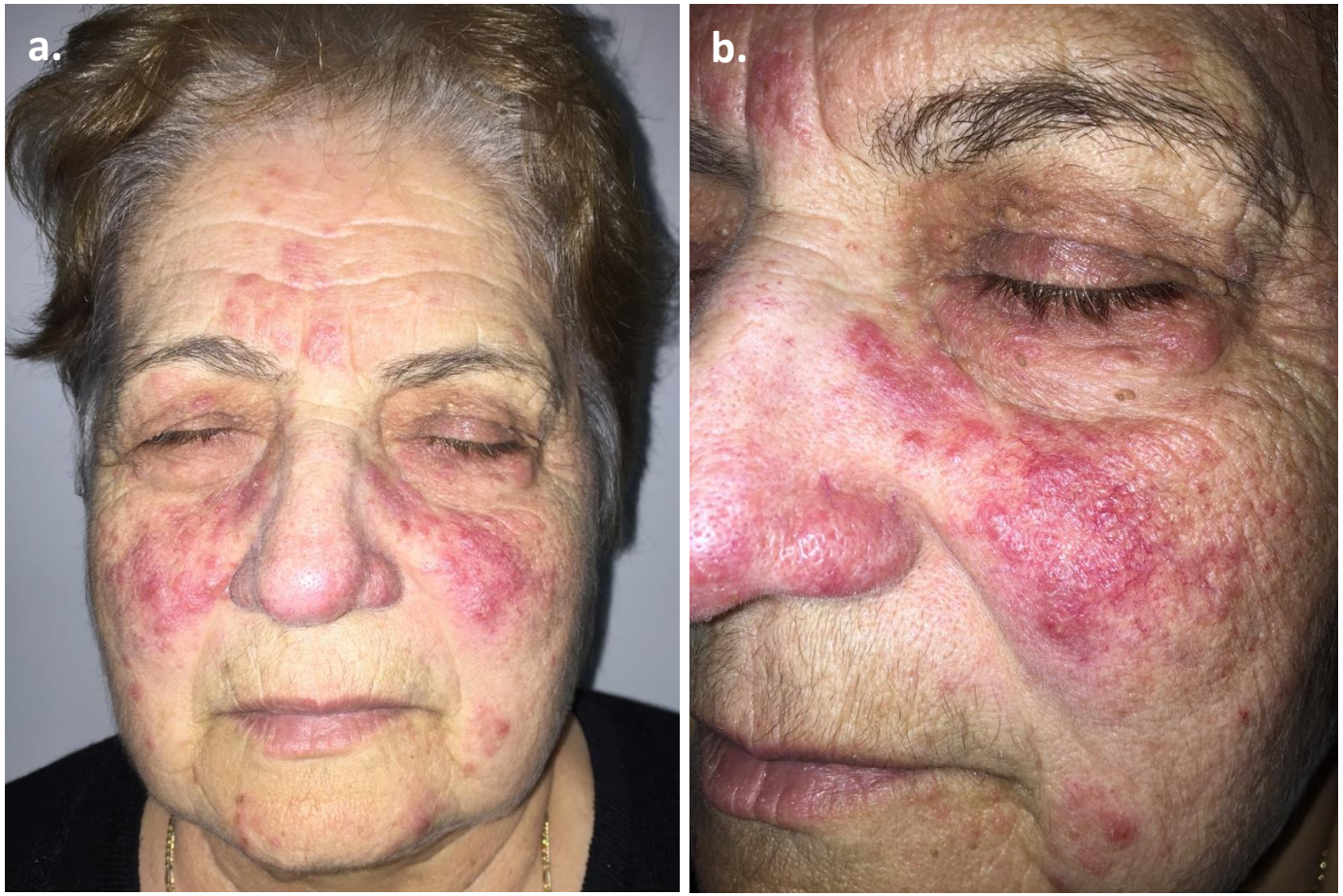

Figure 1. A 62-years-old female with erythematous eruptions in a butterfly rash pattern after treatment with adalimumab. Note also a mild periocular and forehead erythema. Figure 1a, b: malar eruption or “butterfly rash” (erythema and oedema of cheeks, sparing the nasolabial folds). Figure 1b shows the skin findings in more detail.

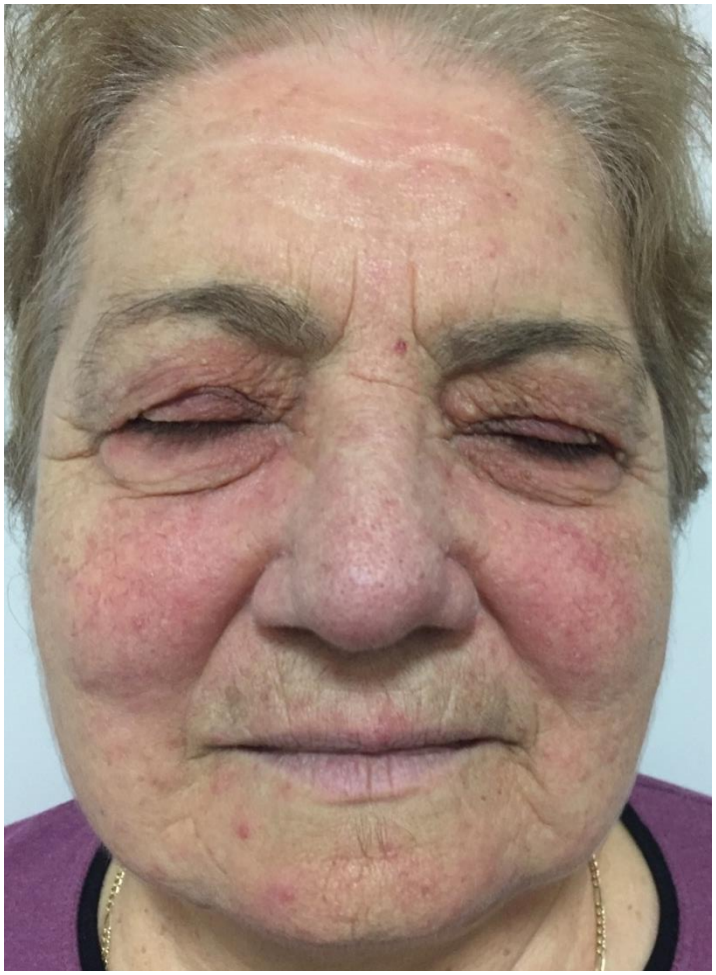

Figure 2. The same patient five months after discontinuation of the anti-TNF (adalimumab) treated with small doses of steroids and topical calcineurin inhibitors. Note that the cutaneous eruptions have been improved and there is only a mild erythema with no new skin lesions.

Kaltsonoudis et al. Arthritis Research & Therapy 2014, 16:R125
http://arthritis-research.com/content/16/3/R125

arthritis research&therapy

RESEARCH ARTICLE Open Access

Neurological adverse events in patients receiving anti-TNF therapy: a prospective imaging and electrophysiological study

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Review

Demyelination and other neurological adverse events after anti-TNF therapy

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Materials and methods

102 pts with RA and SpA eligible for anti-TNF were treated

According to the disease demands (possibility of response to the therapy) and personal preferences of our patients, after their informing about the dosage schemes

All patients gave their approval to participate in the study

Clinical and paraclinical screening

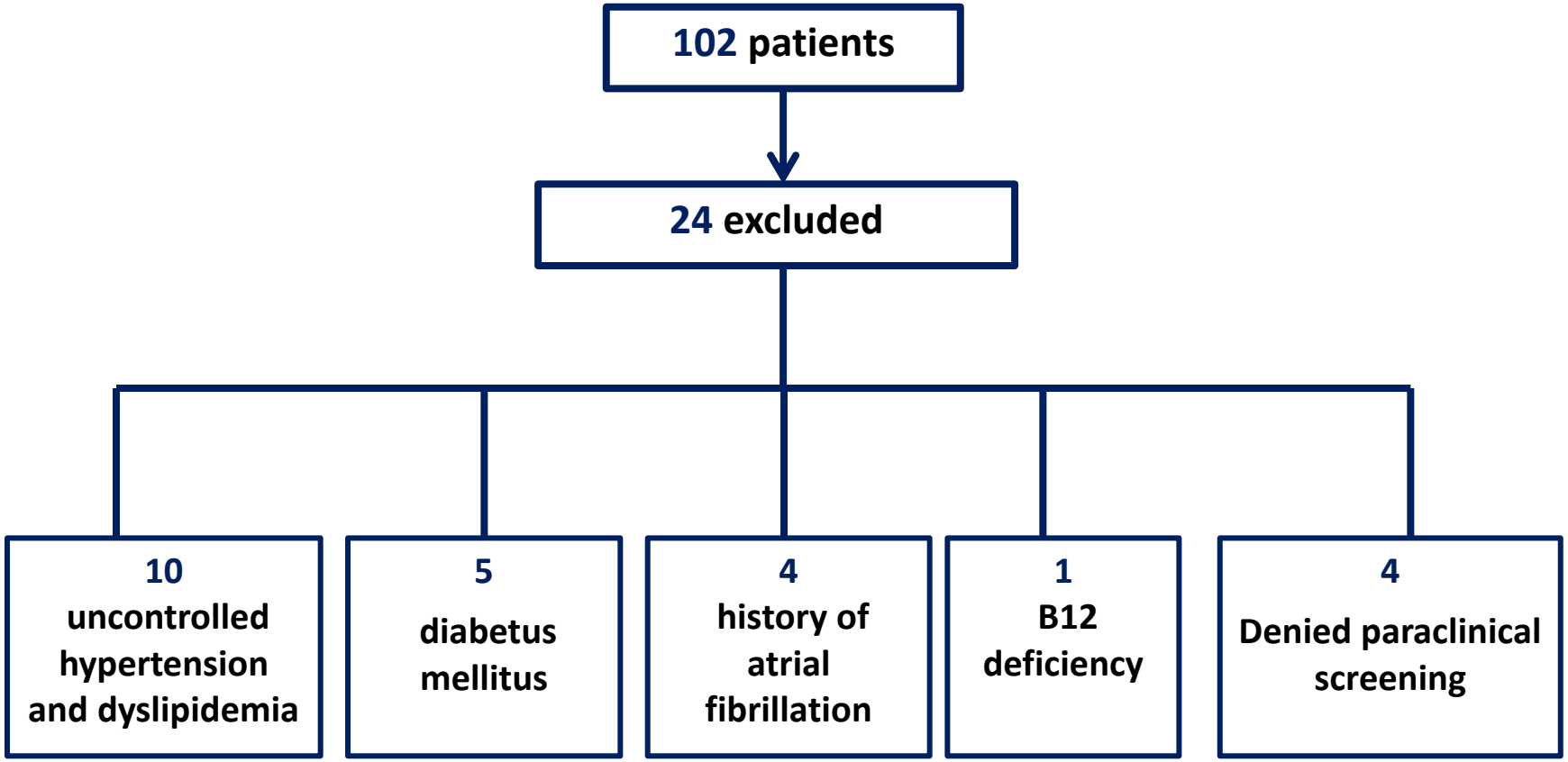
Before starting

- All patients had full physical examination
- Detailed neurologic evaluation
- Brain and Cervical Spine MRI were also performed
- Neurophysiological tests (neuron conduction speed - electroneurogram [ENG])

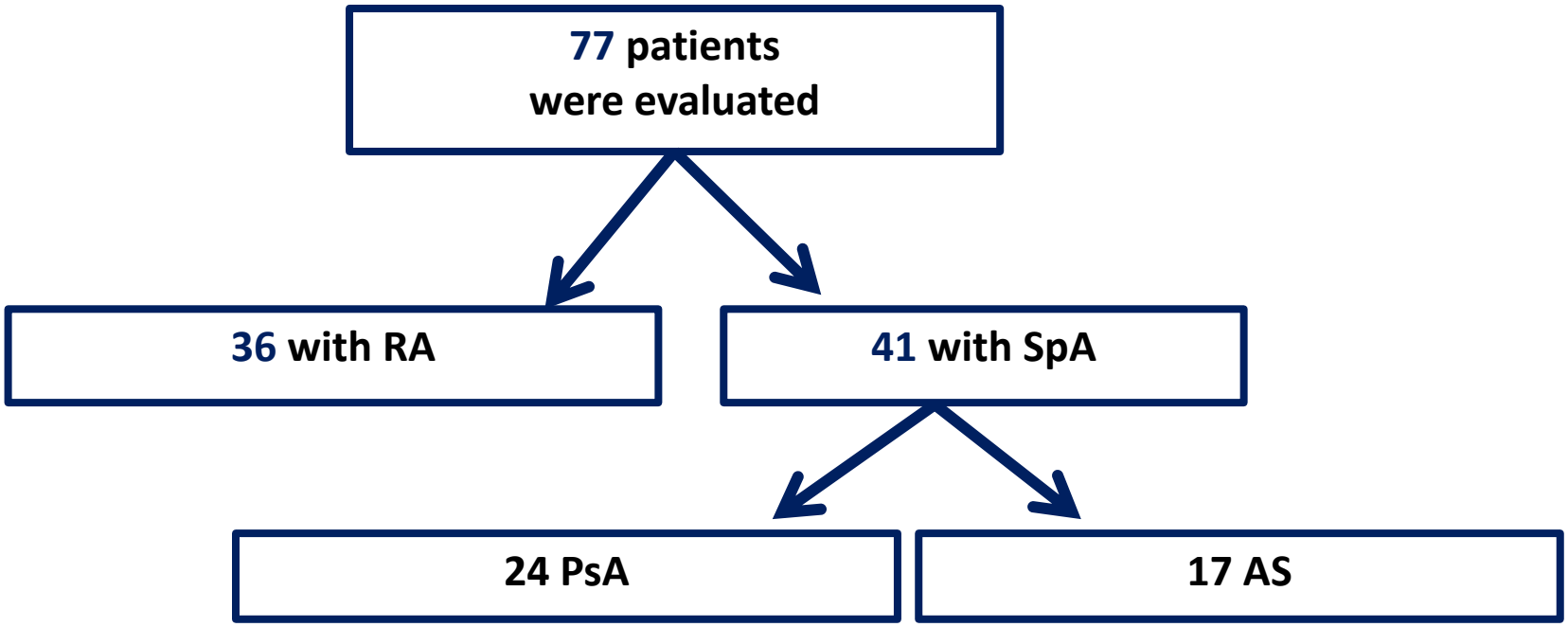
Exclusion criteria

- Patients with severe uncontrolled hypertension
- Diabetus Mellitus
- Dyslipidemia
- History of atherothrombotic events
- Cardiac arrhythmias
- B12 deficiency
- Iron deficiency
- Patients with history of head or cervical spine injury
- And any other neurological comorbidities

Study protocol



Study protocol



Immunology tests

All patients, before starting the therapy, had immunology tests

- Antinuclear antibodies (ANA)
- Double stranded DNA helix antibodies
- Antibodies against cardiolipin (ACL)
- β2GPI antibodies
- Lupus anticoagulant (LA)

Table 1 Demographic characteristics of patients eligible for anti-TNF therapy

Variable	Value
Patients, n	**77**
Male/female, n	42/35
Average age, years, n (SD)	55.3 (12.5)
Rheumatoid arthritis patients, n (%)	36 (46.8)
Psoriatic arthritis patients, n (%)	24 (31.2)
Ankylosing spondylitis patients, n (%)	17 (22.1)
DMARDs intake, n (%)	55 (71.4)
Methotrexate, n (%)	31 (56.4)
Cyclosporin, n (%)	10 (18.0)
Leflunomide, n (%)	4 (7.0)
Steroids intake, n (%)	12 (15.6)
Anti-TNF intake, n (%)	75 (97.4)
Infliximab, n (%)	38 (51.0)
Adalimumab, n (%)	19 (25.0)
Etanercept, n (%)	18 (24.0)
Antinuclear antibodies positivity, n (%)*	10 (13.0)
Rheumatic factor positivity, n (%)*	28 (36.4)
Anti-citrullinated antibodies positivity, n (%)*	29 (37.7)

*Refers to the total number of the patients in this study.

Kaltsonoudis E, et al. Arthritis Res Ther 2014;16:R125

Before the onset of the anti-TNF-α therapy

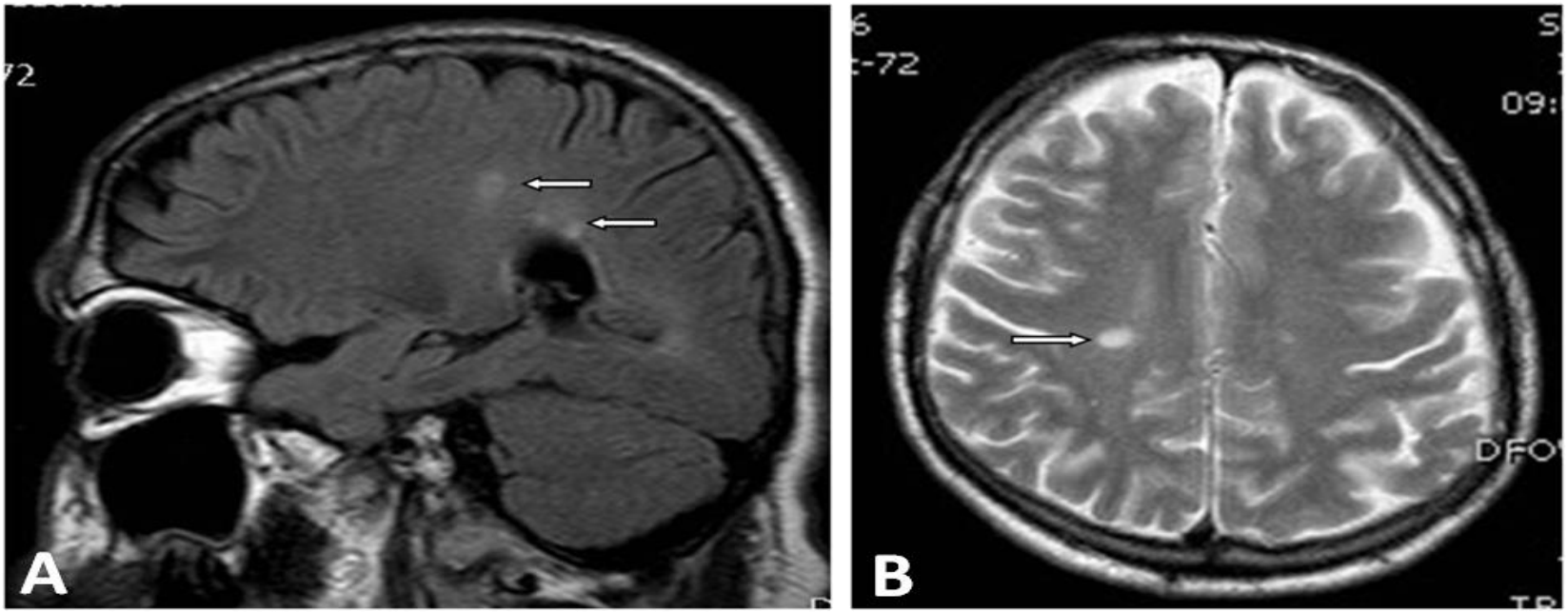
- A patient with AS complained for numbness at the left arm and dizziness
- The neurological examination, the Brain and Cervical spine MRI and the neurophysiological tests

Did not show any pathological findings and the patient received ant TNF therapy

- Two patients, a male aged 35 with AS and a woman aged 46 with PsA

Never received anti – TNF – α therapy because of MRI pathological findings

Lesions in brain MRI before therapy onset (male aged 35 with AS)



Flair sequence in sagittal plane (A) and T2 sequence (B) in transverse plane show spindle – shaped high signal lesions at the periventricular white matter (arrows)

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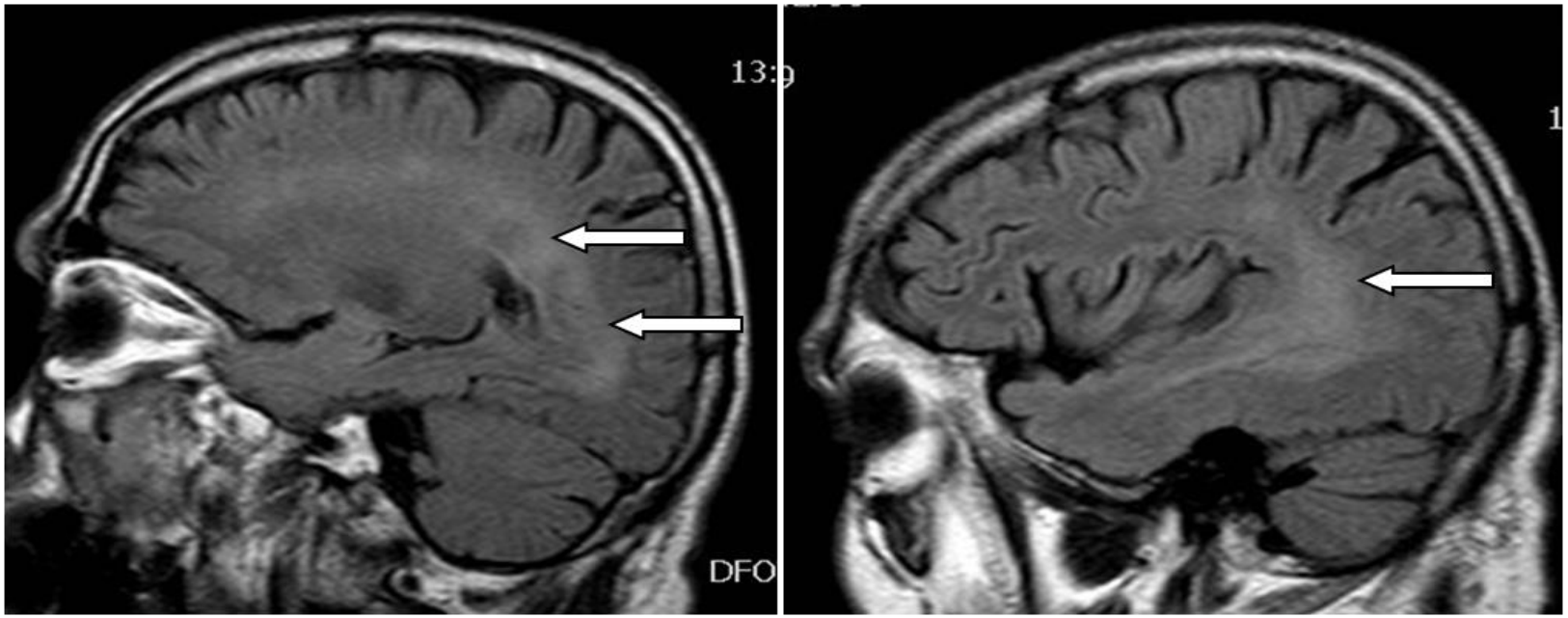
Lesions in brain MRI before therapy onset (female aged 46 with PsA)



Flair sequence in sagittal plane (A,B) shows diffuse high signal at the periventricular white matter in the parietal, occipital and temporal lobe (arrows)

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Before the onset of the anti-TNF-α therapy

- Except for the one patient with PsA whose medication was modified from etanercept to infliximab (due to insufficient response after a 10-month therapy)
- The rest of the 74 patients received anti-TNF-α for the first time
  - 38 patients received Infliximab
  - 19 Adalimumab
  - 18 Etanercept
- Mean duration of follow – up: 18 months, [between 16 and 26 months]
- 3 patients developed neurological complications

1st case

- Male aged 35 with PsA for many years
- With a long term follow – up in our department
- With peripheral small and large joint involvement, and axial involvement (sacroiliitis)
- Also, diffuse skin involvement (PASI score >10)

Course of the disease

- Initial treatment with DMARDs : Methotrexate and Cyclosporine A
- Because of insufficient response, Etanercept was started
- No major additional benefit and after 8 months infliximab was started

Course of the disease

8 months after treatment with Infliximab

- He came complaining about:
  - Difficulty speaking
  - Difficulty swallowing
  - Left mouth corner drop
  - Numbness and paresthesia at left lower limb
- Laboratory routine tests were normal
- Immunologic tests (ANA, ACL, β2GPI και LA) were negative

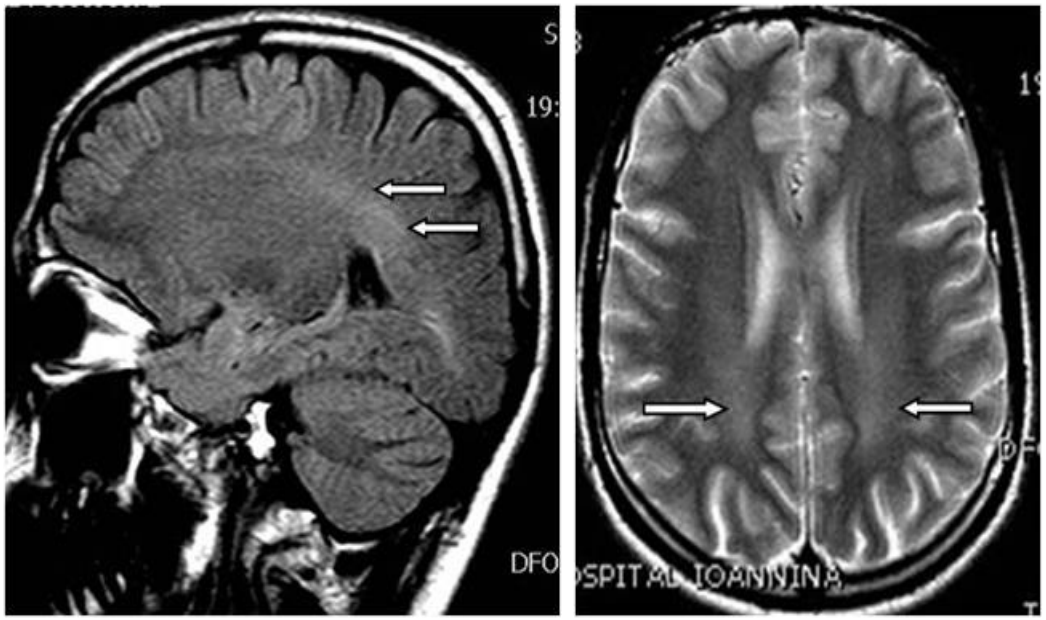
Course of the disease

Neurological examination showed:

- Paresis of the left facial nerve
- and ipsilateral paresis of the fibular nerve

Cervical spine and Brain MRI showed lesions compatible of apomyelinotic disease

1st case: lesions in brain MRI



Flair sequence in sagittal plane (A) και T2 sequence (B) in transverse plane highlight a diffuse high signal in the periventricular white matter at the parietal and the occipital lobe (arrows).

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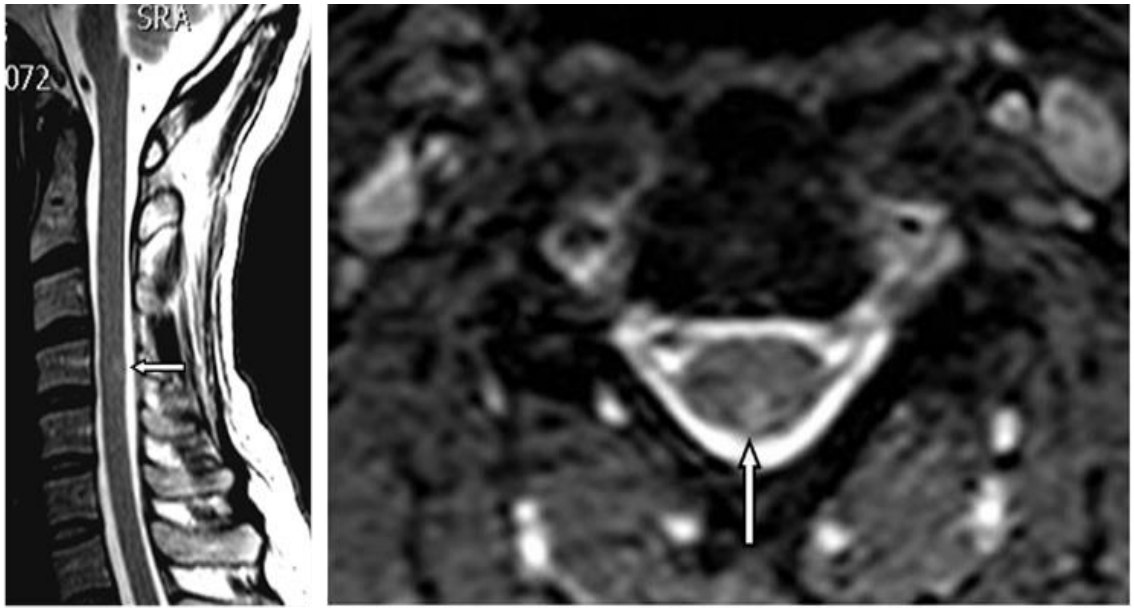
1st case: lesions in cervix MRI



T2 sequence in sagittal (Γ) and transverse (Δ) plane of the spinal cord shows a small lesion with peripheral localisation

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Neurological disease therapy - restoration

- The neurophysiological study of the lower limbs showed left fibular nerve paresis and active fasciitis
- Infliximab was discontinued and the patient was submitted for intravenous injections of methylprednisolone (1 gr / day for 5 days) with significant clinical improvement
- Full restoration of the neurological symptoms occurred gradually two months later

2nd case

- Female aged 45 with RA
- Treatment with MTX + HCQ
- Good clinical response for one year, when he relapsed
- Then, Adalimumab was started with very good clinical and laboratory response

2nd case

- After 6 months of Adalimumab therapy
- Came to us because of pain and low visual acuity of the right eye
- Neurological and eye examinations were normal
- Brain MRI had no pathological findings
- Diagnosis: optic neuritis based on clinical examination

Course of the disease

- Adalimumab was discontinued
- Without additional treatment
- Restoration came gradually (two months later)
- In this period, RA symptoms relapsed

Course of the disease

- Based on the disease state
- And after the written compliance of our patient
- Adalimumab, was re-administered
- A month later and while the underlying disease (RA) was under satisfying control
- A second episode of optic neuritis came up, this time in the left eye

The drug was discontinued once and for all

3rd case

- Female aged 50
- Diagnosis: Ankylosing Spondylitis
- Joint Involvement: Sacroiliac joints & Spine
- Co-morbidity: Crohn’s disease (for the past 5 years)
- With insufficient response to synthetic DMARDs

3rd case

- We administered: Infliximab 5 mg/kg/BW
- Three months later remission of both diseases
- After 25 months of Infliximab therapy she presented

Numbness and paresthesias of both lower extremities

Course of the disease

- Neurological examination showed impairment of tendon reflexes and lower limb hypoesthesia
- Brain MRI showed no pathological findings
- ENG showed significant reduction of sensory conduction speeds

Course of the disease

- Infliximab was stopped
- We administered Gabapentin 1600 mg / daily

Some improvement of sensory symptoms were noted

- 3 months after Infliximab discontinuation

Severe AS symptoms relapsed

Rheumatoid arthritis

Risk of neuroinflammatory events in arthritis patients treated with tumour necrosis factor alpha inhibitors: a collaborative population-based cohort study from Denmark and Sweden

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Conclusions Use of TNFi in AS/PsA, but not in RA, was associated with increased risk of incident neuroinflammatory disease, though the absolute risk was below one in 1000 patients/year.

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Neuroinflammatory events after anti-TNFα therapy

We have read with interest the article by Kopp *et al* that has been published recently in the Annals of the Rheumatic Diseases. The article deals with the risk of neuroinflammatory events (NIEs) in patients with inflammatory arthritides (IA), receiving tumour necrosis factor alpha (TNFα) inhibitors.[1] Their cases were identified from the nationwide registries of Sweden and Denmark, in a prospective observational study. The authors found an increased risk of NIEs after anti-TNFα therapy in patients with spondyloarthropathies (SpAs) as compared with those not receiving TNF blockers, while no consistent and significant risk of NIEs after anti-TNFα treatment in rheumatoid arthritis (RA) patients. They concluded that the risk profile of NIEs in patients receiving TNFα inhibitors differs among patients with different IA which has an impact on decision-making in clinical practice.

In a prospective imaging and electrophysiological study of our clinic, patients with RA and SpAs who were eligible for anti-TNFα therapy had been investigated, during the period May 2009 to December 2011.[2] Before starting anti-TNFα therapy all patients had a full physical examination and a detailed neurological evaluation. In addition, all had brain and cervical spine MRI and neurophysiological studies with nerve conduction velocity and needle electromyography (EMG) of the upper and lower extremities. Patients with severe and uncontrolled hypertension, diabetes mellitus, dyslipidaemia, history of atherosclerotic events, heart arrhythmias, B12 and iron deficiency as well as patients with a history of head and cervical spine injury had been excluded from the study. From a cohort of 101 patients, 24 had been excluded. From the remained 77, there were 36 with RA and 41 with SpA (24 psoriatic arthritis (PsA) and 17 ankylosing spondylitis (AS)). Before the onset of therapy one patient with AS complained for numbness of the left arm and dizziness. The neurological evaluation, as well as brain and cervical spine MRI and neurophysiological studies, showed no abnormalities and the patient received anti-TNF therapy. On the other hand, two patients without any objective clinical manifestations never received anti-TNFα therapy because their brain MRI showed pathological findings compatible with multiple sclerosis (MS) (figure 1A). These two patients with brain MRI and suggestive findings of MS but without MS symptoms are classified as having radiological isolated syndrome (RIS) which is considered to be a preclinical MS syndrome.[3] Finally, 75 patients received anti-TNFα therapy. All patients were naïve to TNFα inhibitors except one patient with PsA who was switched from etanercept (ETN) to infliximab (INF) due to primary inadequate response. During follow-up (mean period 18 months) three patients manifested NIEs. More specifically: the patient with PsA who switched from ETN to INF developed clinical symptoms and signs compatible with MS after a period of 8 months. The findings were confirmed by MRI and electrophysiological studies. One patient with RA treated with adalimumab (ADA) developed optic neuritis after 9 months of treatment. Finally, another patient with AS and Crohn's disease receiving INF developed sensorimotor peripheral neuropathy after 24 months of INF treatment. The estimated rate of NIEs in our study was 4% (3/75). But, if we also calculate the incidental MRI findings of RIS in those two additional patients, the estimated rate of NIEs arises to 6.66% (5/75) leading to a p value of <0.00001 (significant at $p<0.05$). This means, that we may treat a clinically asymptomatic patient (RIS patient) with an anti-TNFα agent and as a consequence, the patient may finally develop a NIE.

We believe that the autoimmune phenomena like NIEs that develop during anti-TNFα therapy, are agent-depended and not disease-depended meaning that these are a class-effect phenomenon.[4 5] Indeed, new autoimmune NIEs have been described. Two patients with RA, one receiving ETN[6] and another treated with ADA developed myasthenia gravis syndrome.[7] Thus, in patients which are candidates for anti-TNFα therapy, in order to avoid NIEs a detailed neurological evaluation is mandatory. In addition, a close follow-up and an appropriate monitoring with MRI and EMG are also essential when indicated.

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Contributors All four authors have made substantial contributions to the current manuscript and more specifically: EK: acquisition of the data and analysis as well as approval of the final version. EP: drafting, data analysis and approval of the final version. AAD: conception of the work, review and approval of the final version. PVV: review and approval of the final version.

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CASE BASED REVIEW

Adalimumab-induced myasthenia gravis: case-based review

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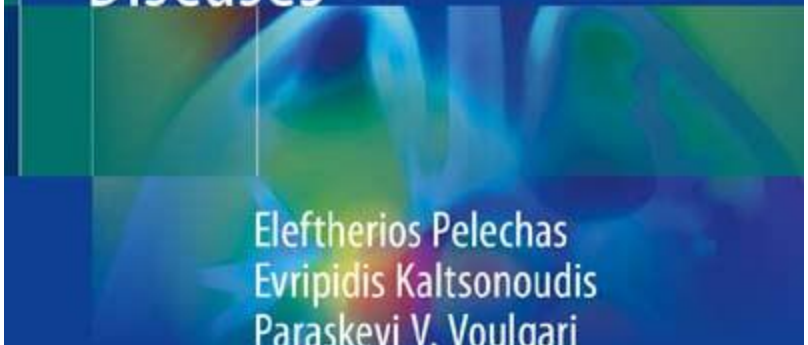
Fig. 1 Neostigmine test is a pharmacological test demonstrating the clinical improvement of patients with myasthenia gravis. **a** Shows a patient with myasthenia gravis with eyelid ptosis of the left eye. **b** Demonstrates the clinical improvement with eyelid elevation after neostigmine test

Illustrated Handbook of Rheumatic and Musculo-Skeletal Diseases



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Conclusions

- The use of biologic agent have revolutionized the treatment of inflammatory of autoimmune diseases
- However the use of these agents may alter the immune function and its response
- It can manifest as immunodeficiency such as infection, or as autoimmunity such as paradoxical inflammation or autoimmune diseases
- Understanding the immunological mechanisms of these side effects will improve their use and improve the outcome for the patients
- Thus, physicians dealing with patients treated with biologic agents should be aware of possible development of autoimmune diseases. Close monitoring is required

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