ΑΡΘΡΙΤΙΔΑ ΚΑΙ ΜΥΟΣΙΤΙΔΑ ΣΕ ΑΣΘΕΝΗ ΜΕ ΚΑΡΚΙΝΟ ΠΝΕΥΜΟΝΑ

Παγκοπούλου Ελένη

Ειδικευόμενη Ρευματολογίας

Κλινική Ρευματολογίας και Κλινικής Ανοσολογίας

Πανεπιστημιακό Γενικό Νοσοκομείο Λάρισας

ΑΙΤΙΑ ΠΡΟΣΕΛΕΥΣΗΣ

Άνδρας 63 ετών παραπέμπεται από τους θεράποντες ογκολόγους για αρθρίτιδα γονάτων αμφοτερόπλευρα και έκπτωση της μυϊκής ισχύος των κάτω άκρων

- Αδενοκαρκίνωμα πνεύμονα
  - ανοσοθεραπεία (pemprolizumab) από 9/2017 έως 6/2018

ΑΤΟΜΙΚΟ ΙΣΤΟΡΙΚΟ

- Στεφανιαία νόσος (PTCA και Stenting)
  - Υπό acetylsalicylic acid
- Εν τω βάθει φλεβοθρόμβωση (προ 2μήνου)
  - Προστέθηκε rivaroxaban
- Πρώην καπνιστής (70 pys, stop 2006)

ΚΛΙΝΙΚΗ ΕΞΕΤΑΣΗ

- ΑΠ=132/89mmHg, SatO2=99%, Σφ=69/min, θ=απύρετος
- Μυοσκελετικό: ***αρθρίτιδα γονάτων (δεξιά >> αριστερά) , μυϊκή ισχύς 4/5***
- Μη ψηλαφητοί περιφερικοί λεμφαδένες
- Δέρμα: χωρίς εξάνθημα
- Καρδιά: S1, S2 ρυθμικοί, ευκρινείς
- Κοιλία: μαλακή, ευπίεστη, ανώδυνη, μη ψηλαφητά ήπαρ και σπλήνας, ήχοι παρόντες
- Αναπνευστικό σύστημα: αναπν. ψιθύρισμα ομότιμο αμφοτερόπλευρα

ΔΙΕΡΕΥΝΗΣΗ ΑΣΘΕΝΟΥΣ 1

ΕΞΕΤΑΣΗ	ΤΙΜΗ ΜΕΤΡΗΣΗΣ
ΓΕΝΙΚΗ ΑΙΜΑΤΟΣ	
WBC	11.300
Hct	35,4
Hgb	11,6
PLT	254.000
ΒΙΟΧΗΜΙΚΟΣ ΕΛΕΓΧΟΣ	
Ur	28
Creat	0,54
AST	20
ALT	22
CPK	133
ΔΕΙΚΤΕΣ ΦΛΕΓΜΟΝΗΣ	
ESR	73
CRP	4
ΕΛΕΓΧΟΣ ΓΙΑ ΛΟΙΜΩΔΗ	
Wright - Coombs	Αρνητική

ΕΞΕΤΑΣΗ	ΤΙΜΗ ΜΕΤΡΗΣΗΣ
ΕΛΕΓΧΟΣ ΠΡΩΤΕΙΝΩΝ	
RF	<10.60
C3	129
C4	23,9
ΑΝΟΣΟΔΙΑΓΝΩΣΤΙΚΟΣ ΕΛΕΓΧΟΣ	
ANA	1:160
P-ANCA	Αρνητικά
C-ANCA	Αρνητικά
Anti-CCP IgG	Αρνητικά
Anti-SSA (Ro)	Αρνητικά
Anti-SSB (La)	Αρνητικά
AMA	Αρνητικά
ASMA	Αρνητικά

ΔΙΕΡΕΥΝΗΣΗ ΑΣΘΕΝΟΥΣ 2

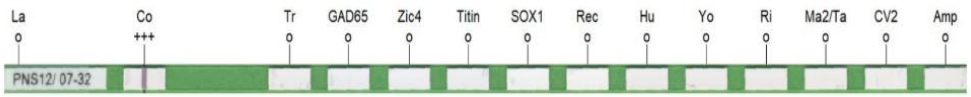
- Α/α γονάτων : χωρίς αλλοιώσεις
- Αδυναμία παρακέντησης (λήψη αντιπηκτικής αγωγής)
- ΗΜΓ : Αυτόματη δραστηριότητα πρόσθιου κνημιαίου δεξιά και γαστροκνημίου δεξιά ⟶ Μυοσίτιδα

ΔΙΑΦΟΡΙΚΗ ΔΙΑΓΝΩΣΗ

Αρθρίτιδα και Μυοσίτιδα

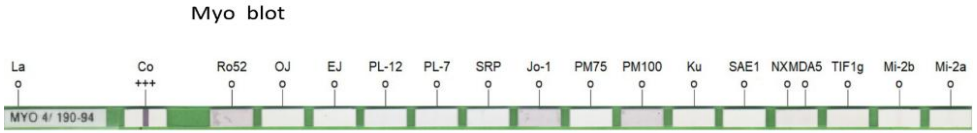
- *Παρανεοπλασματική εκδήλωση?*

Paraneo blot



- *Πρωτοεμφανιζόμενο αυτοάνοσο?*

Myo blot

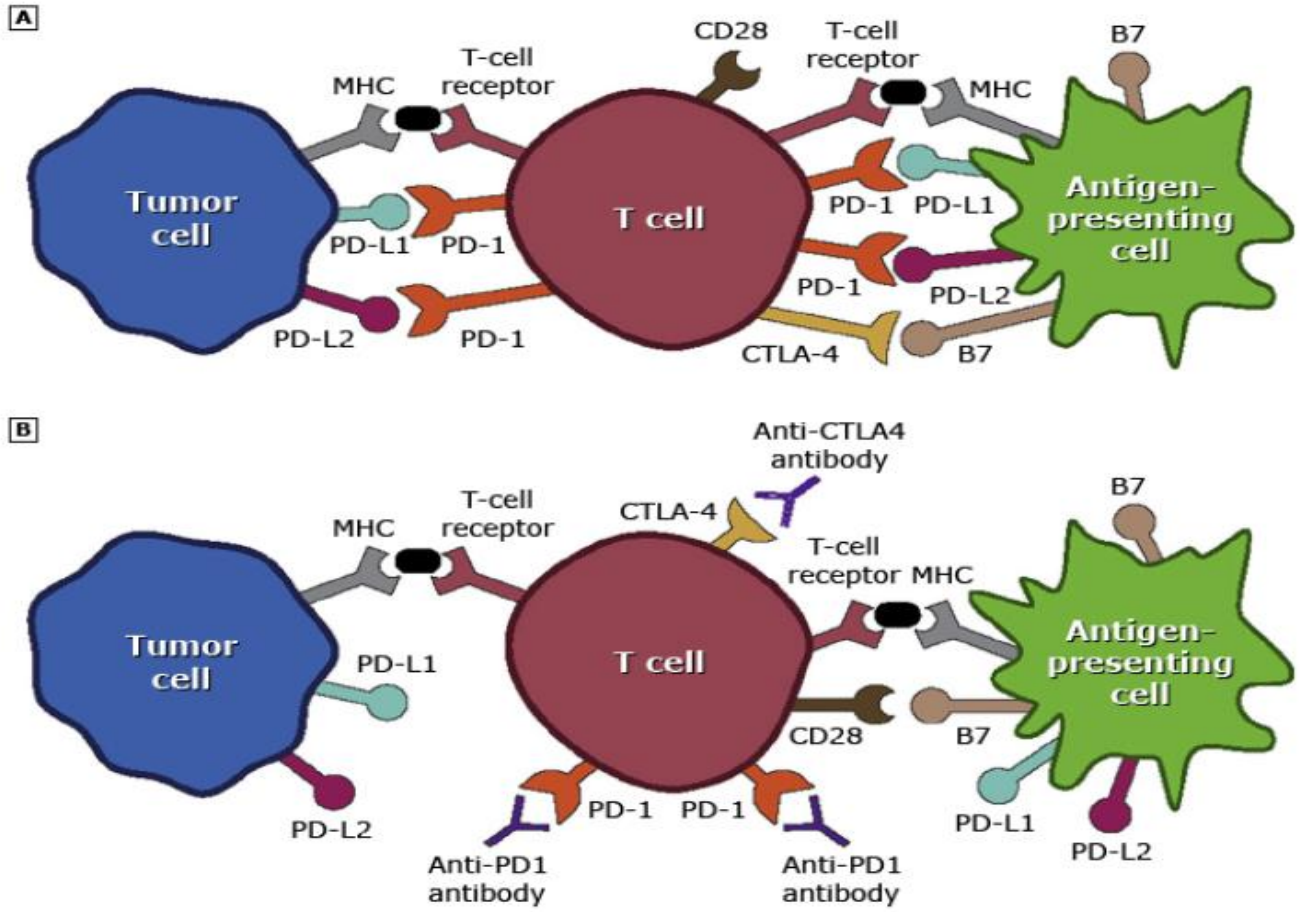


- *Ανεπιθύμητη ενέργεια ανοσοθεραπείας?*

Rheumatic irAE	Rheumatic disease comparator	Similarities to rheumatic disease	Differences from rheumatic disease
Inflammatory arthritis	RA	• Can cause erosive disease • Many patients with similar joint distribution (MCPs, PIJs, wrists and knees)	• Tendon involvement more prominent early in course of disease • Early erosions • RF and CCP often negative • Not female-predominant
Inflammatory myopathy	Dermatomyositis, polymyositis and immune-mediated necrotizing myopathy	• Range of creatine kinase is 10–100 IU/l (upper limit of normal) • Biopsy results are consistent with dermatomyositis, polymyositis or immune-mediated necrotizing myopathy • Can have myasthenia with myositis	• Classic dermatomyositis rash rare • Response to intravenous immunoglobulin may be less effective in irAE

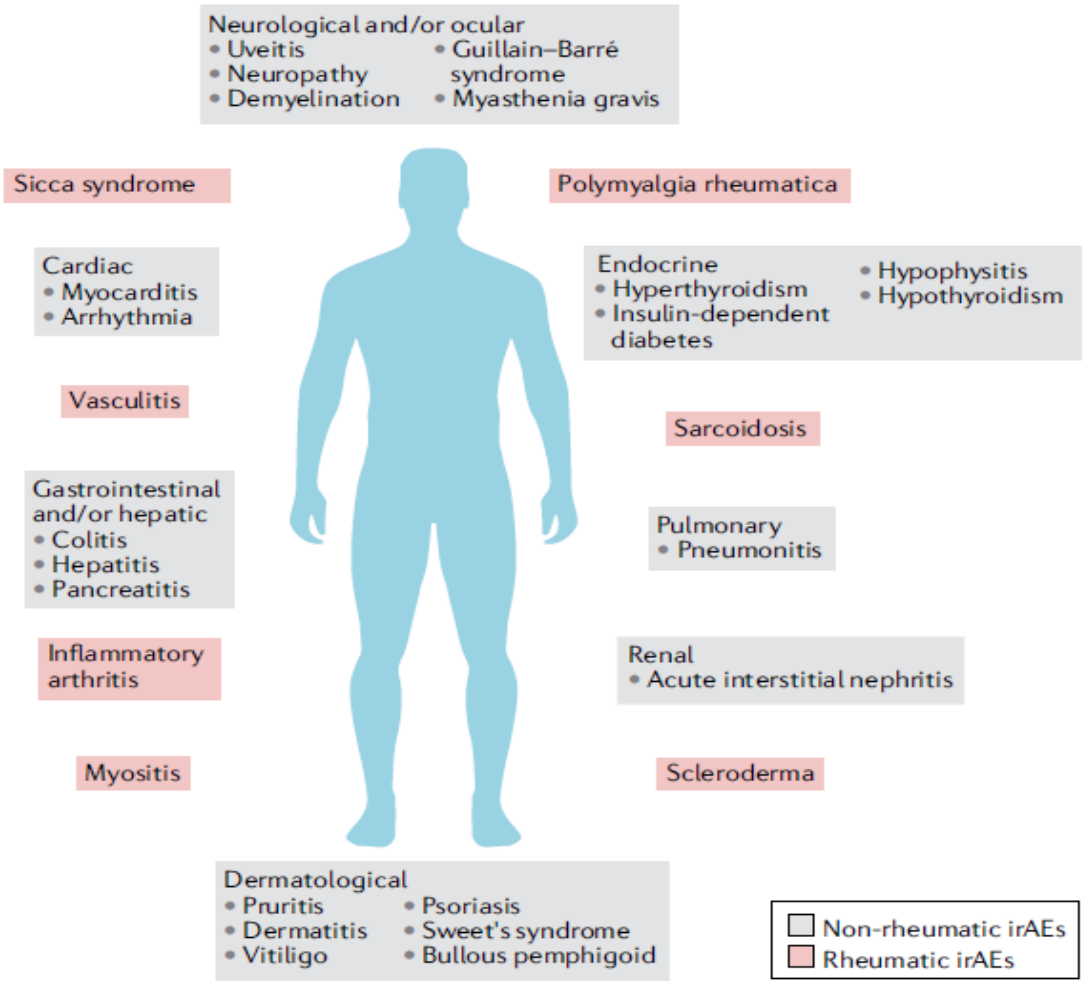
Calabrese LH, Calabrese C, Cappelli LC (2018) Rheumatic immune-related adverse events from cancer immunotherapy. Nature Reviews Rheumatology 14:569-579

ΜΗΧΑΝΙΣΜΟΣ ΔΡΑΣΗΣ PEMBROLIZUMAB



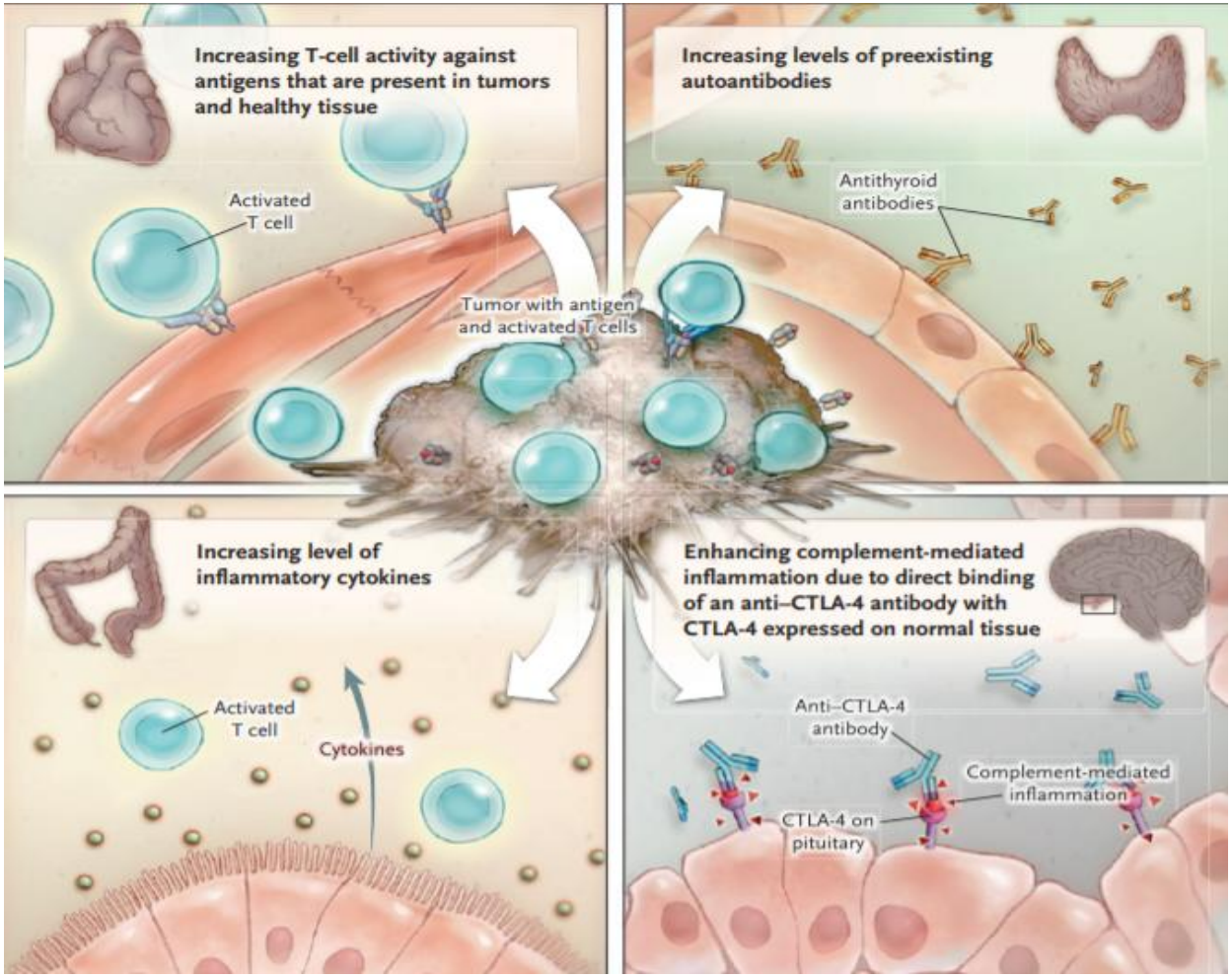
Cappelli LC, Shah AA, Bingham CO III. Immune-related adverse effects of cancer immunotherapy — Implications for rheumatology. Rheum Dis Clin N Am 2017; 43:65.

IMMUNE – RELATED ADVERSE EVENTS (irAEs)



Calabrese LH, Calabrese C, Cappelli LC (2018) Rheumatic immune-related adverse events from cancer immunotherapy. Nature Reviews Rheumatology 14:569-579

ΠΙΘΑΝΟΙ ΠΑΘΟΓΕΝΕΤΙΚΟΙ ΜΗΧΑΝΙΣΜΟΙ



Postow MA, Sidlow R, Hellmann MD (2018) Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. New England Journal of Medicine 378:158-168

Management of inflammatory arthritis

Grading	Management
All grades	Clinicians should follow reports of new joint pain to determine whether inflammatory arthritis is present; question whether symptom new since receiving ICPi
G1: Mild pain with inflammation, erythema, or joint swelling	Continue ICPi Initiate analgesia with acetaminophen and/or NSAIDs
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental ADL	Hold ICPi and resume upon symptom control and on prednisone ≤ 10 mg/d Escalate analgesia and consider higher doses of NSAIDS as needed If inadequately controlled, initiate prednisone or prednisolone 10–20 mg/d or equivalent for 4–6 weeks If improvement, slow taper according to response during the next 4–6 weeks; if no improvement after initial 4–6 weeks, treat as G3 If unable to lower corticosteroid dose to < 10 mg/d after 3 months, consider DMARD Consider intra-articular corticosteroid injections for large joints Referral to rheumatology
G3–4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to G1 or less Initiate oral prednisone 0.5–1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD Synthetic: methotrexate, leflunomide Biologic: consider anticytokine therapy such as TNF-α or IL-6 receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment Referral to rheumatology.

Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(17):1714–1768

Management of myositis

Grading	Management
G1: Mild weakness with or without pain	Continue ICPi If CK is elevated and patient has muscle weakness, may offer oral corticosteroids, and treat as G2 Offeranalgesia with acetaminophen or NSAIDs ifthereare no contraindications
G2: Moderate weakness with or without pain, limiting age-appropriate instrumental ADL	Hold ICPi temporarilyand may resume upon symptom control, if CKis normal and prednisone dose < 10 mg; if worsens, treat as per G3 NSAIDs as needed Referral to rheumatologist or neurologist If CK is elevated three times or more), initiate prednisone or equivalent at 0.5–1 mg/kg May require permanent discontinuation of ICPi in most patients with G2 symptoms and objective findings (elevated enzymes, abnormal EMG, abnormal muscle MRI or biopsy)
G3–4: Severe weakness with or without pain, limiting self-care ADL	Hold ICPi until G1 or less while off immune suppression and permanently discontinue if any evidence of myocardial involvement Consider hospitalization for severe weakness Referral to rheumatologist or neurologist Initiate prednisone 1 mg/kg or equivalent. Consider 1–2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia) Consider plasmapheresis Consider IVIG therapy Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4–6 weeks; rituximab is used in primary myositis but caution is advised given its long biologic duration

Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(17):1714–1768

ΘΕΡΑΠΕΙΑ

1. Πρεδνιζολόνη 20mg/day
2. Μεθοτρεξάτη 10mg/week

TAKE HOME MESSAGE

- Immune checkpoint inhibitors ⟶ irAEs
- Απαιτείται συνεργασία μεταξύ ογκολόγων και ρευματολόγων

ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ