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## The general practitioner and rheumatic manifestations of malignant tumors

### Key words:

rheumatic diseases,  
rheumatic manifestations,  
neoplasma

### Abstract

The doctors in general medical practice meet, diagnose and treat different patients in their everyday practice. Some of those patients belong to the group “polymorbid ones”, which is not so easy to manage and requires a multidisciplinary approach. Rheumatic diseases occupy a large percentage of this type of work. Osteoarthritis is the most common rheumatological disease in general practice and it reaches 40% of all people who consult their general practitioner (GP) with joint complaints. But apart from such well-known and convincingly presented diagnoses, the GPs see some other rheumatic problems that are harder to diagnose and understand. One of the examples of such rheumatic pathology, especially interesting for us, is the “rheumatic mask” of malignant processes, i.e. different solid tumors and malignant hemopathies. A delayed diagnosis in those cases makes treatment harder and outcome – not good.

Rheumatology is an interdisciplinary branch of the medical science, which overlaps with many other branches. In about 3-7% of the patients with rheumatologic manifestations there is actually a mask of some malignant process, i.e. paraneoplastic rheumatic syndromes<sup>1</sup>:

There are difficulties in patients with a rheumatic mask of a malignant process concerning:

- the early diagnosis of the neoplasma
- the differential diagnosis

The reasons for development of such an overlap between rheumatology and oncology (cancerogenesis) are as follows<sup>2</sup>:

- infections (viral and others)
- chemical factors
- immune mechanisms
- genetical predisposition

The infectious factors are outlined on table 1.

**Table 1.** Role of viral agents in cancerogenesis and development of rheumatic diseases

Viruses	Rheumatic diseases	Malignant processes
HBV, HCV	SLE, PAN, Cg	Ca hepatitis, B-cell lymphomas
EBV	SLE, PSS, Sjogren's syndrome	Lymphoma, Hodgkin's disease, Nasopharyngeal Ca
CMV	SLE, PSS, Sjogren's syndrome	
Parvovirus B19	Arthritis	Oncohematological diseases
Retrovirus – type 5	SLE, Sjogren's syndrome.	Leukemias, lymphomas, sarcoma
HTLV-1	Sjogren's, PM	T-cell lymphomas

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When discussing the pathogenesis, cancerogenesis and immunogenesis one can include:

- the theory of molecular mimicria: similar antigen determinants
- the T cellular immunity which is impaired in T-cell leukemias and autoimmune rheumatic diseases
- the role of the suppressor-genes (oncogenes like the p53 gene and their mutations)<sup>3</sup>

Chemical factors are the second group of factors and they may induce some of the following:

A. Oncology – cancerogens influence mutations, e.g. aniline, smoking, etc.

B. In rheumatology chemical factors may cause development of sclerodermic manifestations

C. Postchemotherapeutical drug syndromes – they appear 2-16 months after the end of chemotherapy and include myalgias, arthralgias, drug-induced lupus, progressive systemic sclerosis.

The third group is the one of immune factors. More than 400 autoantigens, tumor-suppressing genes and antigens like Sm, Jo and others were proven to participate in the process. The role of anti-inflammatory cytokines is also to some extent uncovered (IL1, TNF-a, IL-17...)<sup>4</sup>

It is good to find out which comes first – the tumor or the rheumatic disease. There are differences in different cases. One possibility is when the tumor precedes the rheumatic syndrome<sup>5</sup>. This may happen in rheumatic syndrome with paraneoplastic genesis; local invasion of tumor cells affecting the musculoskeletal system; as a side effect of chemotherapy. Rheumatic diseases and conditions may appear first, i.e. develop before the neoplasma and present a risk factor for the latter<sup>6</sup>.

The most common rheumatic manifestations of malignant tumors include:

- Arthritis
- Myositis
- Fasciitis
- Periartthritis
- Systemic diseases, like paraneoplastic dermatomyositis

It is important for GPs to be aware of the two main tasks that arise when they meet a paraneoplastic rheumatic syndrome (established or probable):

- To prove the neoplasma on time if there is one.
- To have an adequate attitude towards the management of the rheumatic syndrome itself

This means to decide what to use and in what dose – corticosteroids, NSAIDs, analgetics, physiotherapy, other types of therapy.

Paraneoplastic rheumatic syndromes may include<sup>7</sup>:

- Tumor-associated arthritis
- Palmar fasciitis, contractures, periartthritis (Carcinoma ovarii)
- Panikulitis, subcutaneous nodules, serositis (Pancreatic carcinoma)

- Hyperurikemia and gout (sometimes after polychemotherapy)
- Hypertrophic osteoarthropathia /Carcinoma pulmonum)
- Shoulder-hand syndrome (Carcinoma pulmonum)

Another option to consider are the systemic manifestations and vasculitises<sup>8</sup>:

- Paraneoplastic polymyositis / dermatomyositis
- Paraneoplastic scleroderma syndrome
  - local forms
  - pseudoscleroderma
- Raynaud syndrome and digital necrosis
- SLE-like syndrome: polyarthritits, polyserositis, positive tests for ANA and anticardiolipin antibodies
- RA-like syndrome, with serositis, RF positivity
- Polymyalgia rheumatica
- Vasculitis (for example, leucocytoclastic vasculitis).

Apparently we must look for haematological findings in all malignant processes. Those findings include but are not limited to anaemias (hemolytic; iron-defficiency), thrombocytopenia, thromboembolia, DIC syndrome, cryoglobulinaemia.

As a whole, the general practitioners managing people with rheumatic complaints should bear in mind the possibilities for etiology outside of the musculoskeletal system.

Tumor-associated arthritis seems like RA but there are some differences. Firstly, the course of the disease is atypical. Also, there is asymmetry in the joint involvement together with a late age of onset (more than 60 usually). It usually starts from the lower extremities and not from the hand joints. In addition, RF is negative, no rheumatic nodules are found. If a biopsy is done, no specific changes will be discovered. The table below may help in differentiating this syndrome both in men and in women.

**Table 2.** Tumor-associated arthritis<sup>9,10,11</sup>

MEN	WOMEN
<ul style="list-style-type: none"> <li>• acute start in older men</li> <li>• seronegativity (RF +/-)</li> <li>• synovitis</li> <li>• weight decrease</li> <li>• no effect from corticosteroids</li> <li>• Ca pulmonum, Ca colonis</li> </ul>	<ul style="list-style-type: none"> <li>• middle age usually</li> <li>• most complaints – from the hands</li> <li>• periartthritis</li> <li>• Dupuytren contractures</li> <li>• fasciitis</li> <li>• Ca ovarii, lymphoproliferative diseases</li> </ul>

The hyperurikemia and possible gout are explained by the purines going to the blood stream after tumor cells undergo necrosis because of different reasons. The level of uric acid is parallel to the severity (the mass) of the tumor. Hyperurikemias are more often seen in lymphoproliferative processes and also in hepatic carcinomas. Together with that, in case of insufficient hydratation, there will be higher levels of calcium and potassium.

Hypertrophic osteoarthropathy is yet another possibility. A differential diagnosis with idiopathic forms is required. Hypertrophic osteoarthropathy is a syndrome of clubbing of the fingers, periostitis of the long (tubular) bones, clock glass nails and arthritis. Paraneoplastic growth factors stimulate the osteoblasts which is a main point in pathogenesis.

## Conclusion

We stated that rheumatic symptoms and syndromes can be an early clue for a developing malignant process (both solid tumors and hemopathies), so a GP's preparation is essential. GPs' good level of knowledge in oncology and rheumatology is the key to early diagnosis and more favorable outcomes for such oncologic patients.

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## Лекар опште медицине и реуматске манифестације малигнух тумора

### Кључне речи:

реуматска болест,  
реуматске манифестације,  
неоплазме

### Сажетак

Лекари опште медицине у својој свакодневној пракси сусрећу, дијагностикују и лече различите пацијенте. Неки од тих пацијената спадају у групу полиморбидних пацијената, који захтевају мултидисциплинарни приступ и није их лако лечити. Реуматске болести заузимају велики део ове врсте рада. Најчешћа реуматска болест у општој медицини је остеоартроза, која је заступљена код 40% пацијената који се јаве лекару због тегоба у зглобовима. Али осим ових, добро познатих и убедљиво презентованих дијагноза, лекар опште медицине виђа и друге реуматолошке проблеме које је теже дијагностиковати и разумети. Један од примера такве реуматске патологије, која је посебно интересантна за нас, јесте и „реуматска маска“ малигнух болести, односно тумора и малигнух хемопатија. Касно постављена дијагноза у овим случајевима чини лечење тежим, а исход – рђавим.

## Литература

### References

1. Ashouri JF, Daikh DI. Rheumatic manifestations of cancer. *Rheum Dis Clin North Am.* 2011 Nov; 37(4):489-505.
2. Jesus G, Bakcelos A, Neves C et al. Rheumatic manifestation and neoplasms. *Acta Rheumatol Port.* 2006 Oct – Dec; 31(4):305-21.
3. Racanelli V, Pretl M, Minoia C et al. Rheumatic disorders as paraneoplastic syndromes. *Autoimmun Res.* 2008 May; 7(5):352-8.
4. Dorronsoro MI, Merino MR, Sastre-Urguelles A et al. Malignant disease presenting as Rheumatic manifestations. *An Pediatr.* 2004 Nov; 61(5):393-7.
5. Abu-Shakra M, Biskila D, Ehrenfeld M et al. Cancer and autoimmunity: autoimmune and rheumatic features in patients with malignancies. *Ann Rheum Dis* 2001 May;60(5): 433-41.
6. Fam AG. Paraneoplastic rheumatic syndromes. *Baillieres Best Pract Res Clin Rheumatol* 2000 Sep;14(3):515-33.
7. Reuss-Borst MA. Rheumatic and hemato / oncological disorders. *Z Rheumatol.* 2005 Feb; 64(1):3-11.
8. Marengo MF, Suarez-Almazor ME, Lu H. Neoplastic and paraneoplastic synovitis. *Rheum Dis Clin North Am.* 2011 Nov;37(4):551-72.
9. Ravindran V, Anoop P. Rheumatic manifestations of benign and malignant haematological disorders. *Clin Rheumatol* 2011 Sep;30(9):1143 – 9.
10. Kiltz U., Brandt J., Zochling J. et al. Rheumatic manifestations of lymphoproliferative disorders. *Clin Exp Rheumatol.* 2007, Jan – Feb, 25(1): 35 - 9.
11. Mayet W.J. Gastrointestinal tumors. Clinical manifestations of paraneoplastic rheumatic symptoms. *Z Rheumatol* 2011 Sep; 70(7): 567 – 72.

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