Ph.D. DISSERTATION

A STUDY OF TUMOUR RELATED MYOSITIS CHARACTERISTICS.

CLINICAL CLASSIFICATION OF REUMATOLOGICAL PARANEOPLASTIC SYNDROMES

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AIMS and QUESTIONS

1. Examination of tumor associated myositis symptoms and clinical characteristics:
    - What is the frequency of tumor-associated myositis in our patients?
    - What are the diverging clinical characteristics of tumor associated myositis compared to patients with primary myositis ?
    - Do significant tumor associated pathognomic symptoms exist ?
2. Examinations of specific laboratory changes in tumor-associated myositis.
    - Are there laboratory parameters, prognostic factors, which can be used to identify occult tumors?

3. Examination of the genetic background of tumor-associated and primary myositis patients.

4. Treatment possibilities and efficacies.
    - Is there a difference between the treatment of paraneoplastic-originated and primary dermatomyositis ?
    - How does myositis symptoms affect oncological treatments ?

5. Examination of tumor-associated myositis survival rates and prognostic factors.
    - Survey of Mortality

6. A Survey of rheumatological paraneoplasia
    - The main characteristics of diagnosis, etiology and pathogenesis, classifications, and clinical entities.
    - Are there such paraneoplastic symptom groups that can be associated to certain tumors?

- In cases of suspected paraneoplasias, when is examination for tumors warranted?

- **PATIENS AND METHODS**

PATIENTS:

At the Department of Clinical Immunology, 3rd Department of Medicine (University of Debrecen, Medical Center, Hungary), we have been treating medical cases with PM/DM since 1985. Over a median follow up period of 102 months (8-190),we studied the development of malignant diseases in our 309 myositis patients. Our aim was to study the clinical, immunological, and therapeutic characteristics of myositis cases associated with cancer.

METHODS

We retrospectively analyzed clinical and laboratory data of our PM/DM patients in the interval between 1985 and 2006 based on the available data. We analyzed symptoms affecting skeletal muscles, skin lesions characteristic of DM, and the existence of extramuscular manifestations of PM/DM (arthralgia, Raynaud's phenomenon, cardiac involvement, ILD and dysphagia). We determined the presence of anti-Jo-1 autoantibody in the patients' sera. We also examined their therapeutic responses. The diagnosese of PM/DM where made according to criteria set up by Bohan and Peter. Skin and muscle biopsies were performed at the 2nd Departement of Surgery and the Institute of Pathology conducted the histological analysis. Pulmonary involvement was assessed by high-resolution computed tomography (HRCT) at the Department of Radiology. Anti-Jo-1 autoantibodies were determined from sera with ELISA kit (Cogent) at the Regional

Immunology Laboratory of the 3rd Departement of Medicine. In every case, the diagnosese of the malignant disease were based both on histological analysis and clinical examinations.

Statistical analysis was determined using the SPSS for Windows 10.0 statistics software (SPSS Inc., Chicago, IL,USA).The survival curves were drawn using the Kaplan Meier method. A long rank test was used to determine the statistical significance of the observed difference in survival rates between patient groups. We considered a 'p' value to be significant at less than 0,05. Routine statistical methods were used to describe the demographics of the patient groups and to examine the subgroups. Patient groups were compared using the 'Student-type T test', and the 'Fisher-type exact test'.

RESULTS

Between 1985 and 2006, 309 patients with PM/DM were admitted to our Department. 206 of these had PM and 103 had DM. Of the 206 PM patients, there were 7 (3.3%) tumor-paired cases. Tumors were found in 30 of 103 (28.8%) patients with dermatomyositis. 37 of the DM/PM cases (11.9%) cases had myositis paired tumors.

Interval to tumor discovery

Considering the variations in timeline, the DM/PM symptoms in our patients appeared either before, simultaneous to, and in some cases a few years after the appearance of the malignant processes. In 2 patients the two diseases appeared simultaneously, in 6 patients the tumor appeared ≥3 months after the presence of myositis (16,2%), in 11 patients 4-12 months later (29,7%), in 2 patients between 13-24 months

(5,4%), in 1 patient the tumor appeared 3 years after the appearance of myositis (2,7%) and in 6 of our cases more than 5 years (5,6,7,10,20,30 years) elapsed between the appearance of myositis and the tumor (16,2%). In 4 of our cases the diagnosis of the malignant tumor had preceded the appearance of myositis by ≥1 year (10,8), in 2 patients 18 months (5,4%) and in two other patients 72 months have passed between the recognition of the malignant disease and the expression of myositic symptoms (5,4%). In conclusion 64,8% of the tumors developed within the first year of the appearance of myositis (24 patients).

In one case, several primary tumors were diagnosed in the lifetime of a DM patient (occurrence of endometrial carcinoma 16 years prior to myositis, kidney carcinoma was found 2 years prior and at 9 and respectively 11 years after the expression of DM, colon and stomach cancers were found), however, always independently from myositic activity (therefore, the association between the tumors and dermatomyositis is questionable). According to literature, the exact time intervals, definitions of timely associations of myositis and tumor are not well defined. Based on previous population studies (C. Nobuo) and excluding those cases, where too long time elapsed between myositis and tumor we considered tumor associated or paraneoplastic myositis the following cases : if the tumor preceded the myositis less than 5 years, if the diagnosis of cancer was done during the first three years after myositis appearance and if the symptoms of myositis and tumor presented near simultaneously (±1 year). Of the 37 DM/PM patients with tumors described above, 28 corresponded to these more severe criteria, in these situations a paraneoplastic origin is probable. In the remaining 9 cases, tumor paired mysositis is by random.

Age

The average age of our primary DM patient group at the time of diagnosis is lower than that of the TAM patients (we considered baseline the patient's age at the time of diagnosis), and the difference was significant (43,25±12,6 years vs. 57,11±10,06 years). At the same time, it has to be noted, that compared to the average age of all treated IIM patients (40,9±11,6 years), the average age of primary DM patients is higher (43,25±12,6 years). The PM patients are the youngest (39,8±12,01). If we take into consideration the age of all tumor-paired myositis (T+M) patients, this decreases when compared to the population that is considered paraneoplastic (54,28±12,91 vs 57,11±10,06 years).

Sex

In the primary DM/PM patient group dominance of the female sex is typical (2,1/1). This was observed among our TAM patients as well (1,4/1), but the rate of female dominance has decreased. If we are taking into consideration all of our patients who during their lifetime have been affected by both tumors and myositis (T+M), the dominance rate of the female sex increases (1,8/1).

Tumor localisation, pathological subtype

In the case of tumor-associated myositis, we have examined the subtypes of the biopsy of the cancer and the localization of the tumor. Gastrointestinal and breast tumors are common followed by the occurrence of lung tumors: 9 breast, 4 stomach, 5 colon, 5 lung, 2 epipharynx, 1 bladder, 1 ovary, 1 skin, 1 prostate, 2 sarcoma, 1 brain, 1 kidney, 2 lymphatic, 2 endometrial neoplasms. If we disregard those 9 patients in whom there is no

cause-and-effect relationship between cancer and myositis, the following differentiation can be observed in our DM/PM patients. In our 24 DM patients we have found 6 cases of breast cancer, 4 cases of lung tumor, 3 cases of stomach neoplasm, 1 case of intestinal tumor, 2 cases epipharynx carcinoma, 2 cases of Kaposi's sarcoma, 1 case each of cervix, bladder, prostate, brain and ovarial tumor and non-Hodgkin lymphoma have been diagnosed, while in 4 of our PM patients 1 breast, 1 lung, 1 cervix and 1 case of T cell lymphoma developed. In DM cases most common ocurrences were breast, lung and gastrointestinal tumors, and adenocarcinoma was the most commonly found hystological subtype.

Clinical features

We have examined the course, progression and changes of the clinical symptoms in our patients with tumor-associated dermatomyositis and in patients where dermatomyositis was not paired with tumor. Such comparison could not be done in case of PM due to the small number of cancer cases. In both groups the skin lesions characteristic and specific to DM - heliotrop rash (83 vs. 89%), Gotron papule (88% vs. 63%), Gotron sign (68% vs. 51%), V-sign (72% vs. 66%), facial erythema (83 vs. 91 %) – could be observed. It is to be noted, that in cancer associated cases more severe, generally therapy resistant skin changes e.g. ulcerations, itching could be observed (44% vs. 12%, $p<0,05$). Muscle weakness was present in both groups but in the tumor associated group beneath proximal muscle involvement (95 % vs 99 %) distal muscle weakness (57% vs 6%, $p<0,05$) was also present. The muscle weakness of the cancer patients is strikingly severe and frequently is associated with cripling (39% vs. 12%,

p<0,05). Dysphagia (50% vs. 36%) and respiratory muscle involvement (32% vs. 16%) were more frequent in the tumor group and the difference was not significant but the respiratory insufficiency was frequently lethal in this group. The presence of ILD (19% vs. 25%, p=0,043) and cardiac involvement (0 vs. 7%) was also more rare in the cancer associated than in the primary myositis group. Other symptoms - arthritis-arthralgia (16% vs. 51%, p<0,05), Raynaud's syndrome (11% vs. 26 %, p<0,05), fever (0% vs. 29%, p<0,05).

Laboratory caracteristics

The following laboratory examinations were performed: enzimes freed during striate muscle necrosis which are suitable for myositis clinical severity monitoring: LDH, CK; tumor markers (CEA, CA-19-9, CA 72-4, CA 15-3, CA 125, AFP, PSA in males), immune serology markers: (ANF, ENA), myositis specific antibodies. The CK and LDH activity was high in both groups but more elevated levels were observed in the primary myositis group (CK p=0.039 and LDH p=0,047, mean CK ±SD (U/l) – in TAM : 1776±551, in primary DM : 3912±1850, mean LDH ± SD (U/l)- in TAM : 743±234, in primary DM : 1637±764. In TAM cases we measured the CK and LDH levels before and after operation. The decrease in their level was significant, this supports the paraneoplastic origin. CK before operation mean ± SD (U/l) : 2310±646, CK after operation : 110±76; LDH before intervention mean ± SD (U/l) : 1312±820, after intervention : 470±98, p<0,05. The ANF and ENA positivity was significantly more frequent in the primary myositis group (16% vs. 39%, 0% vs. 41%, p<0,05). Presence of anti-Jo-1 antibodies was detectable only in 16% of primary DM cases. In TAM patients this antibody was not present. For cancer screening and follow up purposes after the year

2000 we measured the serum tumor marker levels. The CEA and CA 15-3 is the marker for breast cancer, CEA and CA 125 for ovarial neoplasm, CEA and AFP for liver malignancy, CEA, CA 19-9 and CA 72-4 for gastrointestinal tumor. Significant differences between the two groups were to be measured only in the case of CA 15-3, showing the simultaneous presence of breast cancer. In the case of our colorectal and gastric cancer and myositis patient we did not observe the expected elevated CEA and CA 19-9 serum levels. In patients with prostate tumor the diagnosis was made using rectal digital examination, but the PSA level was not elevated. Due to the low number of patients, statistical evaluation was not performed.

Genetical findings

In order to study the genetic background of myositis, we conducted genetic studies in 145 IIM and 10 TTM patients: the MHC-II. subclass member HLA-DRB1*0301, 01,03 and in relation with it the congenital HLA-DQA1*0501, 01,05 genes, as well as, the ocurrence of HLA-DQBI*2, 03 'alleles' were examined. In the case of DQB1 03 „allele" associations with tumor was found to a great extent. No associatins were found in the case of DRB1 and 01 'alleles'.

Therapeutic observations

Compared to primary myositis, in the case of tumor-paired myositis the use of more agressive treatment protocols were needed. The treatment of the tumor (surgery, chemotherapy, radiotherapy) resulted in the complete recovery of the myositis symptoms in 16 patients. When compared to the 79 primary DM patients, during the treatment of the 28 TAM patients, administering secondary immunosuppressive therapy simultaneous

with, or after the high dose glucocorticosteroid therapy was significantly more often necessary (64% vs. 42%, $p<0,05$). Of the 79 primary dermatomyotisis patients only 46 received steroid therapy, and 33 patients received secondary immunosuppressive therapy (42%). Of the 28 TAM patients 18 received secondary or complimentary aggressive immunosuppressive therapy (64%): Ciclosporin-A 9 patients, IVIG 5 patients, CTX 2 patients, Imuran 5 patients, Methotrexat 2 patients, plasmapheresis 1 patient and 24 patients received steroid therapy (85%). High doses of steroids were needed in 12 patients (42%).

Survival rates. Cause of death

The survival of the tumor-paired cases is determined by the type and stage of the underlying malignant tumor, but the severe myositis symptoms, such as shortness of air also seriously affect the survival prognosis of the patient. According to our results, the one year survival pointers, when compared to the TAM patient group, are significantly higher in the primary IIM group. The one year survival rate in the IIM patient group is 95%, 5 year survival is 92%, while in the case of the 28 TAM patients the one year survival rate is only 86%, and the 5 year is 56%. Examining the survival data of all 37 patients (T+M), these are patients who during their lives had suffered from both myositis and tumor, the one year survival rate was 88%, and the 5 year survival 66%. This proves our suggestion that in the case of 9 of our patients the simultaneous presence of the two diseases happens purely by random, and adding the data of these patients to those in whom paraneoplastic myositis is assumed, the survival data has improved.

In patients where the tumor appeared more or less simultaneously with DM, the course of the disease was more severe than in the cases where the tumor had preceded the appearance of myositis with years, respectively, appeared a few years later. We lost 9 patients out of the 28 TAM patients (32%), one patient due to dissemination of the tumor and involvement of the respiratory muscles, 3 patients due to pneumonia and 2 patients due to shortness of air. One patient died of lung embolia. One of our patients had to undergo surgery due to ileus and that patient died after surgery. One patient died due to heart insufficiency. In the case of six of our cases where breathing difficulties were present, it has to be noted, that in each occasion the tumor and myositis occurred within one year, and despite the intense myositis therapy, the simultaneous existence of both tumor and acute myositis symptoms led to the loss of the patient. The most regular causes of death are thus shortness of air, while in primary IIM the most common cause of death is cardiac in nature, followed by breathing difficulties.

In 16 out of the 28 patients (57%) the tumor was removed surgically, 13 patients (46%) received chemotherapy, and 11 patients (39%) received radiotherapy. 22 patients received some type of active oncologic treatment (78%). In the case of 4 patients oncologic treatments were not possible due to severe shortness of air, these patients died and 2 patients could not undergo antitumor therapy due to overall weakness caused by the spreading of the tumor. Nine out of 28 patients died, 17 are still alive. Years or months after the complete regression of the symptoms, relapse of the myositis symptoms occurred in 5 cases, but no underlying tumor recidive could be proven. In 7 cases the symptoms persisted despite therapy, of these 5 patients died, 16 went into remission.

Classifications and clinical presentations of rheumatological paraneoplastic syndromes

Based on data from the literature and research summaries, the the appearances of reumatological symptoms are grouped by the following classifications:

I. **Systemic autoimmune diseases : 1.** Polymyositis and dermatomyositis**.** 2. Lupus type syndrome. 3. Scleroderma-type syndrome.

II. **Vasculitises:** 1. Atipical polymyalgia rheumatica (PMR). 2. Erythema nodosum. 3. Other vasculitises (e.g. polyarteritis nodosa, temporalis arteritis, Churg–Strauss syndrome, cryoglobulinaemia, Wegener granulomatosis).

III. **Arthropathies:** 1. Hyperthrophic osteoartropathy (HOA). 2. Polyarthritic Carcinoma. 3. Chronic polychondritis. 4. Relapsing seronegative symmetrical synovitis with oedema (RS3PE syndrome). 5. Tumor-associated hyperuricaemia and gout. 6. Palmar fasciitis and polyarthritis.

IV. **Osteopathies:** 1. Reflex sympathetic dystrophia (RSD; algoneurodystrophia; Sudeck-syndrome) 2. Tumor-induced osteomalacia.3.Non-metastastatising hypercalcaemia.

V. **Other locomotor paraneoplasias:** 1. Eosinophilic fasciitis. 2. Panniculitis. 3. Erythromelalgia. 4. Geriatric Raynaud's syndrome.

Myasthenia nad Lambert Eaton syndromes were omitted from the classification, because they are regarded in the literature as neurological paraneoplasias.

DISCUSSION

Totally 309 PM/DM patients had been admitted to our Department. From the 206 patients with PM the disease was associated in 7 cases with tumor (3,3%). Among the

103 patients with DM there were 30 cases in which association with malignancy was observed (28,8%). According to the international literature, the incidence of association of malignant diseases to myositis varies between 7 and 66%. There are only few studies which did not find a relation between PM/DM and malignancy. Bohan and Peter published their diagnostic criteria in 1975, so the results are influenced by the applied diagnostic methods. This is especially true for earlier studies. A further difficulty is posed by the fact that this system is not perfect either, because it requires skin symptoms to determine DM, while the muscle changes of DM can be present with or without cutaneous symptoms. Thus, these cases, which are really DM could easily be diagnosed as PM. The American Academy of Dermatology recommends that DM be confirmed not only by cutaneous symptoms but also by less specific skin symptoms and myositis. In dubious cases they suggest skin biopsy.

Several studies have determined the relative risk (RR) of neoplasm in patients with PM/DM. After meta-analysing four studies, Zantos and colleagues examined 1078 patients with PM/DM and found the RR 4.4 in DM and 2.1 in PM (considering a confidence interval – CI - of 95%). Stockton and colleagues examined the RR of cancer after diagnosing PM/DM with 705 patients and they found 7.7 in DM and 2.1 in PM (CI = 95%). The extent of risk might be influenced by the extensive screen for cancer after diagnosing PM/DM, so the value of RR was determined excluding those patients in whom malignancy was confirmed within 3 months from diagnosing PM/DM. In this way RR was 3.3 in DM and 1.6 in PM . Having summarised and revised the figures of recent cohort surveys carried out in Sweden, Finland and Denmark, Hill and colleagues determined the RR of neoplasm as 3-fold in DM and 1.3-fold in PM (CI 95%) . In these

studies the diagnosis of PM/DM was not always based on histological examinations, so we can suppose that DM cases which were wrongly diagnosed as PM also contributed to the higher risk of neoplasm in PM. On the other hand PM is associated with other types of malignant diseases than DM, so it is likely that PM also has a lower but real risk. Buchbinder examined the risk of malignancy on patients with biopsy-proven IIM. RR was 6.2-fold in DM, 2.0-fold in PM and 2.4-fold in IIM (CI 95%) The association of other forms of IIM with neoplasm are not yet proven by population surveys. According to case reports ADM and other less frequent IIM may associate with malignant diseases.

Literature data and our own results — each of our patients with cancer-associated DM was aged over 45 — also confirm that patients with myositis associated with malignancy are older than the other myositis patients. Although the association of myositis with malignancy is more frequent in older people (> 45 years), the risk is also higher in patients below 45 as compared to the normal population. The mean age in our patient population is 57 years, the youngest patient was 44 years old. The association with malignancy is generally more frequent in females than in males. In our current work, cancer-associated myositis is dominant in women, but compared to IIM the female domination is decreasing. The symptoms of DM/PM developed in 64%-of cases in the same year as the tumor, but in single cases they could be diagnosed with many years before or after the tumor recognition. Paraneoplastic origin is not likely if there are more than 5 years between myositis symptomatology development and tumor diagnosis. In our series the highes risk for tumor recogniton was before 1.5 years and after 3 years of myositis diagnosis.

Although a wide scale of cancer types can be associated with myositis, certain types can be observed more frequently. Ovarian carcinoma lung cancer lymphoma and gastric cancer in adults, while hematologic cancers in children develop more frequently, but other forms of malignancy are also associated, like testicular cancer and thymoma. In the Asian population the most frequent type is nasopharyngeal carcinoma, in which the genetic background and the different nutritional habits may play a role. The epidemiological research carried out by Hill and his team examined a population large enough (1532 myositis patients) to determine the RR for the individual types of tumor. In DM ovarian carcinoma, lung cancer, pancreatic tumor, gastric and colorectal cancer and non-Hodgkin lymphoma (NHL) had the highest RR, whereas in PM the highest RR was shown in NHL, lung cancer and bladder carcinoma. In this study they examined the relation between histological types and found that the highest occurrences in DM were represented by adenocarcinoma and in PM by haematological cancers. In the DM patients in our wards, frequent breast, lung, stomach and epipharinx tumors were observed, which does not conform to previous findings of the Hungarian national registry of tumor's order of prevalence (lung, skin, colorectal, breast). This suggests that there are probably tumour types for which paraneoplastic etiologies with myositis are more prevalent than unassociated malignancies. In DM patients, the most prevalent histological type of tumor was adenocarcinoma. In PM patients, no specific histological tumor types were found.

The malignant disease may precede the myositis or appear simultaneously or follow the diagnosis of myositis within years. The RR of neoplasm is the highest around the time of detecting the myositis and — especially in DM cases — it can remain high for years. The symptoms of DM/PM occurred in 64%of cases in the same year with the tumor. The

role of immunosuppressive agents in the development of cancer comes up especially in the case of malignancy associated with myositis after several years of evolving the myositis. In rheumatoid arthritis azathioprin increases the rate of lymphoproliferative diseases, and cyclophoshamide increases the incidence of bladder cancer. The development of lymphomas was also observed while administering low doses of methotrexate in rheumatoid arthritis. It is interesting to note that Airio found the risk of neoplasm among myositis patients receiving cytotoxic treatment less. In some cases myositis develops after the treatment of the malignant disease, in these instances myositis might be a late complication of the therapy of the cancer (hydroxyurea, IFN-α, bone marrow transplantation).

In 6 of our patients, more than 5 or more years (5,6,7,10,20 and 30years) passed between the diagnosis of myositis and diagnosis of tumors. Of these, 2 patients received Imuran treatment, 1 received cytoxan, 2 received cytoxan, 2 received cyclosporine A, and 1 received steroid treatment. In the case of Imuran, melanoman and colon tumors appeared; after Cytoxan administration, large intestinal cancer appeared and after Cyclosporin A treatment, endometrial and colon cancers developed. In these cases the cancerogenic role of the immunsuppressive treatments can de supposed, despite the fact that according to literature azathioprine favorises lymphoproliferative diseases, cyclophosphamide favorises development of bladder carcinoma, metothrexate favorised presence of lymphomas.

The course of myositis correlates with that of the malignant disease, in the case of effective treatment of the cancer the skin and muscle symptoms of DM rapidly improve

while they worsen when the malignant disease returns. In our study we have looked for the existence of such prognostic factors, which can refer to the simultaneous presence of the malignant disease. Case reports suggest the predictive role of the following factors: old age, therapy-resistant erythroderma, extended or atypical rash, rapidly progressing severe muscle weakness, lack of serological abnormalities and other risk factors of malignant diseases. Gallais and colleagues identified necrotizing cutaneous symptoms and excruciating pruritus as predictive factors. In another study extended skin lesions were more frequent with patients with cancer-associated myositis and also the erythrocyte sedimentation rate (ESR) was higher. Hunger described the significantly more frequent occurrences of cutaneous leukocytoclastic vasculitis in his patients with DM associated with malignancy. In our study severe cutaneous symptoms were observed in 9 out of 12 patients. The Gottron's papules ulcerated and healed very slowly. Proximal limb muscle weakness was present in every patient, arthralgia and dysphagia was equally present in both groups of DM patients. Pulmonary involvement was more frequent in cancer-associated DM. Cardiac symptoms and Raynaud's phenomenon were not observed in the group of cancer-associated myositis .

In these conditions the CK often remains within the normal range and MSA-s among them are more rare. The significant decrease of the CK and LDH values one month after operation supports paraneoplastic origin. Love and colleagues examined the frequency of MSA-s and other autoantibodies and their association with clinical characteristics in 212 patients with IIM. Autoantibodies occurred the least frequently in patients with cancer-associated IIM, the anti-Jo-1 autoantibody, which is the most frequent among MSA-s, did not occur, while the primarily DM characteristic anti-Mi-2 autoantibody was observed in

9% of the sera of cancer-associated patients. The anti-Jo-1 autoantibody could not be identified in the cancer-associated DM group, in the group of DM patients not associated with malignancy anti-Jo-1 positivity was confirmed in 16% of patients. Despite the fact, that some authors consider these tumor markers of having significant prognostic value, this could not be confirmed in our series.

Characteristics of genetic differencies :

Research on genetic backgrounds of myositis is ongoing. Besides genetic factors, family presence is a frequent in certain ethnic groups, as is a myositis / HLA association. In most autoimmune instances, the strongest genetic risk factor are marked by the presence of certain MHC genes. The first publication of such factors were the HLA-B8 from the MHC-I class, and HLA-DR3 from the MHC 2 class genes. According to recent research, there is a tight association between MHC-II class HLA-DRB1*0301 and the inherited HLA-DQA1*0501 genes. The increased incidence of these genes underline the instances in American and European Caucasian patients. In caucasians, the HLA-DQB1*0201 alleles high frequency were found, while afro-americans and latinos carry only the HLADQA1*0501 alleles dominated. In japanese IIM patients dominance of HLA-DRB1*0803, HLA DQA1*0102 és a HLA DQA1*0103 alleles was proven and the protective role of HLA DQA1*0501 gene was observed. We conducted genetic examinations of 145 IIM patients and 10 tumor-associated myositis patients. 10 tumor-associated patients were genetically examined. Due to the small sample size, we were unable to make any conclusions, but on the basis of this data, we were able to conclude that the occurances of HLA DRB1*0301 and 01 alleles showed a reduction of disease but

the HLA DQB1*03 gene showed a domination of disease. In the entire myositis population, there was a dominance of DQA1*01 and *05 genes.

Treatment options, efficacy

Choosing the correct therapies for skin and muscle symptoms of TTM patients is a difficult task. The symptoms are so severe in most paraneoplastic DM cases, that other immunosupressive agents were required in addition to corticosteroid therapy on account of the severity of the symptoms. Significantly more frequent was the need for second line immunosuppressive therapy application during or after large dose gluccocorticoid treatments. The other main aim of tumor treatments is to also have a positive effect on myositis and skin symptoms. Early and correct oncological diagnosis is a primary aim. Partly based on the above, the most important aspect of the diagnosis of myositis related tumors is that the tumor is found as early as possible and the tumorectomy – operation to be performed early as well. If at the same time, myositis is not relieved even after antitumor therapy, aggressive immunosupresive therapy is suggested, as no residual tumors have been known after such occurances.

Examination of tumor associated myositis survival and prognostic factors

While the survival rate of IIM patients continues to improve with modern immunosupressive therapies, use of IVIG, plasmapherises introduction, sensitive diagnostic tools and sophisticated histological approach, the survival rates of TTM patients continues to be quite poor. If there has been no study of this topic using large samples of patients, the reason for this is most likely that the course of background malignancy is unfavourable. Our ward's 56% one year survival expectancy is considered

positive, especially when compared to a recent Japanese study which reported an approximately 10% one year survival of similar patients. This astonishing difference is probably due to the fact that myositis patients have been treated in Debrecen since 1985, and our ward has become the national treatment centre for such diseases. It is very important to examine the existence of tumors in myositis, and especially DM patients. In our ward, for example, in 68% of cases, the two diseases occurred within 1 year, and there is an ongoing risk of tumor occurance remains for 3 years. There is an especially high need for attention to be paid to patients over the age of 50 years.

Timely recognition and treatment of tumors improves prognosis. In our ward, 78% of cases had the possibility of oncological treatment, of which 57% received surgery, 46% received chemotherapy, and 39% received radiation treatment. A major task is the appropriate and timely referral of patients to appropriate oncology centres for the initiation of treatment. Aside from this, it is important for the patient's well being to uphold a constant level of multidisiplinary oversight on the patient.

It can be said that the treatment and recognition of characteristic symptoms of myositis is of utmost importance. Based on our data – especially in cases of older patients – therapy resistance, serious or atypical dermotological manifestations, serious progrediating muscle symptoms are indications of tumor existence. The absence of immunoserological changes may similarly be an indication. Routine measurement of tumormarkers probably does not have a role in diagnosing tumors in myositis patient populations. We recommend examinations, especially of gastrointestinal and breast tumors, in all cases. Recommended basic physical examination, including lymphatic nodule regions and digital rectal examinations, routine blood and enzyme exam, urin and

stool examination (stool benzidine, general and sediment urine analysis). Other basic examinations: chest X-ray, abdominal ultrasound), gynaecological examination (oncocytology, mammography). In the case of myositis patients with serious symptoms, examination of the GI tract (endoscopy), bronchoscopy, CT, MRI and in some cases, a complete PET scan should be considered immediately.

In other cases, prospective examinations are required, in which diagnosis of IIM patients identifying criteria are recognized based on literature characteristics and histology. The goal here is the possibility of standardisation and narrowing the definitions of risk factors, which would be helpful in certain screening examinations. Beside our clinical and laboratory research of Dermatomyositis's of paraneoplastic origin, we also studied all types of rheumatological syndromes that were associated with clinical symptoms of paraneoplastic syndromes. An increasing number of studies support the theory that tumors are often associated with rheumatological symptoms and syndromes. A number of these tumors are of paraneplastic origin, when the tumor itself produces biological mediators, hormones, peptides, cytokines, autocrine and paracrine mediators which are the cause of the symptoms. In clinical practice, it is difficult to differentiate between the manifestations of these various tumor types (e.g. between bone metastasis symptoms, tumorous bones, joint or other similar complaints). The significance of detecting paraneoplastic symptoms in the clinic is great, because it has a large impact on patients' quality of life and life expectancy. Diagnosis of tumors may precede more serious malignancies and alerts physicians to their possibility. Advanced age, serious and rapidly progressing muscle weakness, the appearance of skin symptoms, and serious breathing difficulties are always suspicious indications of tumor presence behind DM

symptoms. It is important to note that in a certain cases, the exact characteristics of paraneoplastic symptoms indicate the location of tumors. For example, in HOA cases, lung tumors are indicated; in cases of vasculitis, myelodysplastic syndromes are indicated; we search after lymphoproliferative symptoms. In DM cases, gastrointestinal tumor screening is highly recommended; in panniculitis cases, pancreascarcinomas tend to occur; and in palmar fasciitis and polyarthritis, gynecological tumors may be present. Thus, it is important to consider that changes in patient's symptoms may reflect changes in their oncological status. Improvement of myositis and rheumotological symptoms often means an amelioration of tumor status and positive reaction to cancer treatment. Conversely, deterioration of symptoms usually indicates the progression of tumors; in cases of tumor reoccurence paraneoplastic complaints and symptoms may reoccur. Unfortunatly, treatment of paraneoplasia is difficult in everyday practice. In most cases, only tumor treatments can cure or improve paraneoplastic symptoms.

A frequent problem is to decide when, in cases of suspected paraneoplasia, to look for tumors. Tumor screeninig is recommended in cases of atypical RA, PMR and late onset Raynaud's symptoms. In cases of acute hand pain, inflammation fasciitis, finger contractures and arthritis, gynecological tumor screening is recommended. In cases of DM, we recommend GI tumor screening before other diagnostic tests. In HOA cases, intrathoracic tumors must be ruled out. Osteomalacia in advanced age indicates tumor screening. In cases of RSD symptoms, tumors should be suspected in occurances of unexplorable trauma, stroke, myocardial infarction are present in the patient's history or if symptoms do not improve with accepted treatments. If the origin of vasculitis is not clear; there is no associated infection or polysystemic autoimmune disease; there is no reaction

to drug therapy; or, if the vasculitis does not react in an expected manner to applied steroid therapy, or to other immunosuppressive therapies, the presence of a tumor must be suspected.

SUMMARY:

Our results are summarized below :

1. Among DM and PM patients, we were most able to recognize malignant tumors in DM patients. Our results indicate that the predominance of female patients among PM/DM cases is lowered when PM/DM is also assotiated with tumors.
2. I was able to show, on the basis of the examinations, that in 64% of cases, the two diseases (tumor and myositis) occurred within one year. As a result, it is important to screen myositis patients for tumors at the time of myositis diagnosis, and continue to monitor patients for the duration of at least one year from the time of myositis discovery. I concluded that the risk of tumor and mysotis association is greatest in the first year, but may occur over 3 years. Tumor symptoms are sometimes recognized first, and in these cases, the risk of myositis is greatest within 1.5 years of diagnosis.
3. Our studies indicate that the most frequent variety of tumor assocated with DM occurs in the breasts, lungs, and GI tract. Histologically, the most frequent form was adenocarcinoma.
4. I brought attention to the fact that clinical research shows that specific to TTM cases are occurrence of serious skin symptoms and frequent ulcerations and skin itching. Muscle weakness is common in both groups, but distal muscle weakness

also occurs and is more frequent in the TTM group and it seriously affects muscles of respiration. Arthritis, arthralgia, Raynaud's syndrome, fever, cardiac manifestations and ILD symptoms were less frequently encountered to be associated with primary myositis.

5. Laboratory examinations indicated that only CK and LDH levels raised in active development of myositis, and were less indicative of tumor associations. CK and LDH values showed significant drops one month after successful tumor removal, which indicates paraneoplastic origins. Immunoserological value changes and myositis specific antibodies occur chiefly in cases of primary myositis. My results indicate that tumor markers are not useful for occult tumor screenings.

6. We concluded, using genetic examinations, that HLA DRB1*0301 and 01 alleles have a preventative effect, while HLA DQB1*03 gene domination is evident in cases of tumor association. We found that the entire myositis population is dominated by DQA1*01 and *05 genes.

7. Analysing the therapuetic specificities I noted that after initial aggressive steroid treatments, myositis associated tumors were frequently in need of immunosuppresants, IVIG and plasmapheresis treatments.

8. I concluded that timely diagnosis of of tumors is of utmost importance. In 78% cases of direct oncological treatments; successful surgery, radiological therapy, and chemotherapy resulted in the improvement of myositis symptoms. I proved that our TTM patients' life expectancy declined compared to primary cases, but were much improved compared to previously published expectancies, which was

explained by the training our clinic has had due to our frequent encounters with myositis patients, early tumor recognition, and referral to oncology departments.

9. Based on previously published data, I classified rheumatological types' associated paraneoplastic syndromes, highliting those symptom groups which suggest occult tumor occurances and thus indicate tumor screenings.