Schnitzler syndrome: an under-diagnosed clinical entity

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ABSTRACT

Schnitzler syndrome is considered to be a rare disorder characterized by a monoclonal IgM protein and chronic urticaria that is associated with considerable morbidity. We hypothesized that the syndrome may be under-recognized and patients may be deprived of highly effective therapy in the form of anakinra. We performed a retrospective search of the dysproteinemia database at Mayo Clinic as well as the medical records of all patients with chronic urticaria to determine the true incidence of the disease. We compared patients with the diagnosis of Schnitzler syndrome and those who met the criteria but in whom the syndrome was not recognized. Comparisons between groups were performed and survival curves determined. We identified 16 patients with diagnosed Schnitzler syndrome and an additional 46 patients who met diagnostic criteria. The monoclonal protein was IgMκ in 94% of patients. Therapy with anakinra in 4 patients led to rapid and complete resolution of symptoms. The median overall survival for this syndrome is over 12.8 years. Progression to lymphoma was only observed in 8% of patients; this is lower than previous reports. Schnitzler syndrome may be present in up to 1.5% of patients with a monoclonal IgM in their serum and likely under-recognized as a clinical syndrome.

Introduction

Between 1972 and 1974, Schnitzler reported on the association between chronic urticaria and an IgM monoclonal protein that ultimately led to the recognition of a distinct clinical syndrome that bears her name.[1,2] Subsequently, the diagnostic criteria were put on a more secure footing by Lipsker *et al.*[3] and then endorsed by the Schnitzler Syndrome Study Group.[4] However, most of these studies included a small number of patients from single institutions and included case reports from the literature to better define the syndrome. This approach carries several risks: on one hand, various clinical features may be missed due to reporting bias, while at the same time, it introduces an inevitable element of clinical heterogeneity that results from the assimilation of patients from different institutions. The typical lag time between the onset of symptoms and diagnosis is of the order of five years.[5] In the absence of a specific diagnosis, these patients suffer significant morbidity due to their symptoms. Given that therapy with the interleukin 1 (IL-1) receptor antagonist anakinra is associated with rapid and long-lasting improvement in symptomatology,[6-9] higher awareness of this syndrome is required. To address the potential problems associated with referral bias, as well as to test the hypothesis that the condition is often unrecognized, we performed a single institution analysis of patients with an established diagnosis of Schnitzler syndrome as well as a search for other patients who met the diagnostic criteria but in whom the diagnosis had not been established.

Methods

Patient identification and data abstraction

We adopted two search strategies to identify our patients and test our hypothesis. i) The first search of all the medical records looked for the term "Schnitzler syndrome" as the key word in the diagnosis. This search identified 16 patients and the medical records of these patients were reviewed and the relevant data abstracted to make sure they meet the diagnostic criteria for the syndrome.[3,5] ii) We performed a second search of the medical records for all patients seen at Mayo Clinic between 1972 and 2010 who had 'chronic urticaria' included as a major diagnosis. We then cross-referenced this list of patients with the dysproteinemia database that includes all patients with an identified monoclonal protein and seen at our institution during the same time interval. The analysis was restricted to patients who had an IgM monoclonal protein identified by immunofixation, in keeping with the diagnostic criteria established by Lipsker.[3,5] Patients who met the diagnostic criteria for multiple myeloma, macroglobulinemia, amyloidosis or another lymphoproliferative disorder were excluded. Note that all the patients who had an established diagnosis of Schnitzler syndrome were independently identified in the second search, implying that our search strategy was exhaustive. After exclusion of the 16 patients who already had an established diagnosis of Schnitzler syndrome, this second cohort was composed of 46 patients. All patients had given informed consent for their medical records to be used for research purposes and the study was approved by the Institutional Review Board at Mayo Clinic Rochester in keeping with the Declaration of Helsinki and federal regulations (HIPAA).

Statistical analysis

Comparisons between nominal variables were performed with the χ^2 test while comparisons between medians for continuous variables were performed with the Mann-Whitney test. Survival analysis was performed using the Kaplan-Meier method with appropriate censoring. The log rank test was used to determine the statistical significance of the difference in survival between cohorts. The impact of various parameters on overall survival was determined using Cox's proportional hazard method. Overall survival was determined from the time

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of diagnosis of the syndrome, or criteria for the syndrome and death or last contact with the patient. All *P* values had to be below 0.05 to be statistically significant. All statistical analyses were performed using StatView (SAS Institute, Cary, NC, USA).

Results

In the interval between 1st January 1972 and 31st December 2010, we identified a total of 16 patients with a primary diagnosis of Schnitzler syndrome. Of these, 10 patients were male and the median age at the time of diagnosis was 66 years (range 43-89). The median time from the onset of symptoms to the diagnosis was five years (range 0-20). By definition, chronic urticaria and a monoclonal protein were present in all patients (major criteria for diagnosis). The most common symptoms were fever (75%), fatigue (75%), arthralgia (68%), bone pain (63%) and night sweats (25%). Palpable lymphadenopathy was present in 44% of patients and the spleen and/or liver were enlarged in one patient (Table 1). There was evidence of a peripheral neuropathy in 56% of our patients.

In Table 2 we summarize the laboratory findings of this cohort of patients. At the time of diagnosis, most patients were anemic (median hemoglobin of 11.7 g/dL) and had leukocytosis (median leukocyte count 11.7). Most patients had evidence of an acute phase response with an elevated erythrocyte sedimentation rate and C-reactive protein. However, the serum ferritin was invariably within the normal range in our cohort. A skin biopsy was performed in 16 patients and this was always compatible with the diagnosis of Schnitzler syndrome (neutrophilic urticaria). The monoclonal protein was an IgMκ in 15 patients (94%) while another patient had an IgMλ. The prevalence of the kappa light chain restriction in this syndrome is disproportionate to what is expected purely by chance. In patients with monoclonal gammopathy of undetermined significance (MGUS), the kappa to lambda light chain ratio is typically 56-44%[10] while in this series, the ratio was 15:1 (*P*=0.0044). The serum M-spike was generally small with a median of 0.6 g/dL. Only one patient had a reduction in IgG (515 mg/dL) with all other patients having normal IgA and IgG levels. These findings are similar to what has been reported in the literature.[3,4] None of our patients diagnosed with Schnitzler syndrome had any detectable cryoglobulins or deficiency of C1-esterase inhibitor. No patient had low levels of C3 (normal range 75-175 mg/dL) or C4 (normal range 14-40 mg/dL), effectively excluding hypocomplementemic urticarial vasculitis. A bone marrow biopsy was performed on 13 patients and the median plasma cell burden was 4%. No chromosomal abnormalities were identified on conventional metaphase cytogenetics or interphase fluorescent *in situ* hybridization. The 'typical' bone sclerosis in the iliac bone was observed in only one patient. Although some patients had a positive antinuclear antibody test (ANA), none had a positive test to anti-double stranded DNA or extractable nuclear antigens or additional criteria to establish the diagnosis of systemic lupus erythematosus.

Most patients were treated with glucocorticosteroids but although approximately two-thirds of the patients responded, these responses were often incomplete and the disease flared as the dose of steroids was tapered. The response to anti-histamines was inferior to that of steroids and the benefit from colchicine or dapsone was limited to one or 2 patients (Table 3). Rituximab was given to 5 patients but only one responded to therapy. Other therapies that were given included non-steroidal anti-inflammatory drugs (4 patients with a response in one), doxepin (no response), and antimalarials (4 patients, none responded). The best outcomes were observed with anakinra (4 patients) with all of these patients having a dramatic, rapid, complete and sustained response. One of these patients reduced the frequency of dosing with anakinra

Table 1. Demographic and clinical characteristics of our two cohorts.

Characteristic	Schnitzler syndrome	Other cohort	P
Gender (M/F)	10/6	22/24	0.47
Age at presentation	66 (43-89)	77 (40-102)	0.02
Urticaria (%)	100	100	N.A.
Fever (%)	75	54	0.16
Fatigue (%)	75	72	0.58
Night sweats (%)	25	58	0.07
Bone pain (%)	63	63	0.95
Arthralgia (%)	68	78	0.47
Angioedema (%)	6	27	0.09
Adenopathy (%)	44	22	0.07
Splenomegaly (%)	6	4	0.76
Peripheral neuropathy (%)	56	20	0.01

Table 2. Laboratory characteristics.

Characteristic	Schnitzler syndrome median (range)	Other cohort median (range)	P
Hemoglobin (g/dL)	11.7 (8.7-15.1)	12.6 (6.5-15.4)	0.41
WBCx10⁹/L	11.7 (4.5-19.8)	8.1 (2.0-28.1)	0.12
PLTx10⁹/L	314 (175-680)	269 (134-615)	0.07
ESR (mm/h)	92 (7-125)	42 (2-130)	0.01
Creatinine (mg/dL)	1.0 (0.6-2.1)	1.0 (0.6-2.3)	0.24
Serum calcium (mg/dL)	9.4 (9-10.1)	9.5 (8.8-10.8)	0.94
C-reactive protein (mg/L)	22.7 (0.4-100)	8.4 (0.3-161)	0.39
Ferritin (mcg/L)	85 (37-328)	68 (7-1898)	0.76
Total complement (μ/mL)	54.0 (18-98)	56.5 (11-126)	0.97
C3 (total), mg/dL	138.5 (86-175)	114 (48-255)	0.08
C4 (total), mg/dL	21.5 (16-55)	22.5 (13-29)	0.56
C1-esterase inhibitor, mg/dL	36 (26-47)	28 (21-37)	0.10
Alkaline phosphatase (μ/L)	143 (46-594)	157 (54-314)	0.60
Beta-2 microglobulin (mcg/mL)	1.8 (1.5-3.5)	2.5 (2.3-2.7)	0.33
BMPC (%)	4.0 (2-13)	5.0 (1.5-48)	0.92
Serum M spike (g/dL)	0.6 (0.1-2.5)	0.8 (0.3-3.9)	0.50
IgM (mg/dL)	549.0 (261-3140)	420.0 (189-7070)	0.37
Monoclonal protein			
IgM kappa	15	34	0.23
IgM lambda	1	9	
IgM Untyped		3	
Bone lesions (imaging)	17	9	0.5

and the symptoms rapidly returned.

We hypothesized that a significant number of patients with Schnitzler syndrome are not being identified. This has become an important issue given the dramatic responses and improvement in Quality of Life once therapy with anakinra is started. To test our hypothesis, we searched the clinical records of all patients seen at our institution between 1972 and 2010 to determine the number of patients who would have met the accepted diagnostic criteria but for whom the diagnosis had not been established. In this time interval, a total of 8439 patients were seen at our institution with a diagnosis of chronic urticaria. Within the same time interval, 4103 patients were found to have a monoclonal IgM in their serum. When we cross-referenced these patients with the dysproteinemia database, restricting the search to patients with an IgM paraprotein alone, we identified an additional 62 patients. Note that all 16 patients diagnosed with Schnitzler syndrome who had an IgM monoclonal protein were also identified through this methodology and, therefore, the search identified 46 new patients. Twenty-three of these additional 46 patients had a skin biopsy performed. None had evidence of cutaneous vasculitis and 5 (21%) had neutrophilic urticarial, as is typical of Schnitzler syndrome. Of these 46 patients, serum protein electrophoresis was repeated in 21 patients several months after the initial identification of a monoclonal IgM in the serum. All showed persistence of the monoclonal protein.

We compared the cohort of patients diagnosed with Schnitzler syndrome with the other 46 patients who had the major criteria for the diagnosis but who had not been diagnosed to determine whether there were any differences between the two groups. The results of these comparisons are summarized in Tables 1-3. As can be seen from the analysis, patients diagnosed with Schnitzler syndrome tended to be younger than the other cohort (median 66 *vs.* 77 years; P=0.012) and they tended to have a higher erythrocyte sedimentation rate (92 *vs.* 42; P=0.01). However, there were no other significant differences between the two groups, suggesting that most of the patients in the second cohort had undiagnosed Schnitzler syndrome as well. We again evaluated the kappa to lambda ratio in this cohort and found 34 of the 46 to be kappa light chain restricted. This skewing towards kappa light chain use was again highly statistically significant when compared to the expected IgM MGUS kappa to lambda ratio (P=0.0089).

Given the lack of any differentiating features, we combined the two cohorts for survival analysis. The median overall survival for all patients is over 12.8 years from the time of diagnosis (Figure 1). A separate analysis comparing the overall survival of the two groups did not find any significant difference (>13.6 years for Schnitzler and >12.8 years for the others; P=0.33). On multivariate analysis, the only determinant of an inferior outcome was the value of

Table 3. Therapeutic approaches in the two cohorts.

Agent	Schnitzler syndrome	Other cohort	P
Glucocorticoids (%)	66.7	35	0.65
Response (%)	66.7	56.2	
Anti-histamines (%)	55	74	0.35
Response (%)	33	35	
Colchicine/dapsone (%)	15	6.5	0.035
Response (%)	14	67	
Rituximab (%)	28	0	
Response (%)	20		
Anakinra (%	23	0	
Response (%)	100		

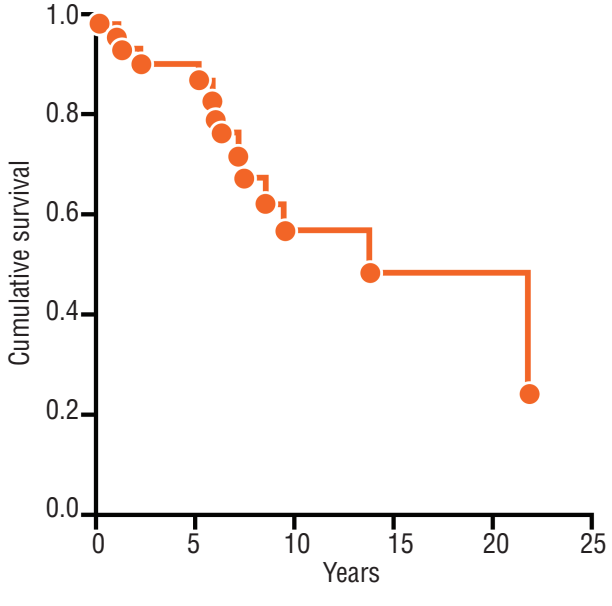

Figure 1. Overall survival for the combined cohort (n=62). For this analysis the 16 patients with Schnitzler syndrome were combined with 46 other patients who met diagnostic criteria.

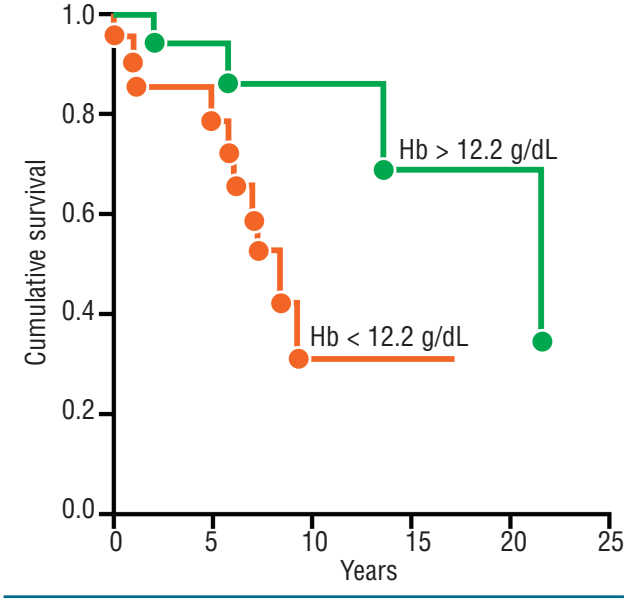

Figure 2. Prognostic impact of hemoglobin at the time of diagnosis. Survival of the 62 patients was analyzed as a function of hemoglobin at the time of diagnosis. Hemoglobin below 12.2 g/dL was the only adverse prognostic factor (P=0.024, log rank test).

the hemoglobin at the time of diagnosis. Patients with a hemoglobin of 12.2 g/dL or over had a survival over 21 years while patients with a hemoglobin less than 12.2 g/dL had a median survival of 8.2 years (*P*=0.024) (Figure 2).

At the time of analysis, only one patient with the diagnosis of Schnitzler syndrome has died, whereas 16 of the 46 other patients have died. The causes of death in the second cohort were: non-Hodgkin's lymphoma in 2 patients, acute myeloid leukemia in one, other cancer in 2 patients, sepsis in one patient, and a cerebrovascular accident in one patient. The cause of death was not available in 9 patients. Therefore, at least 5 patients died as a consequence of a malignancy, including 2 from lymphoma (12%). The cause of death in the one patient with Schnitzler syndrome was not available from the medical records.

Between 1972 and 2010, at Mayo Clinic in Rochester, a total of 4103 patients were identified with a monoclonal IgM in the absence of another related clinical condition and considered to have MGUS. Using this as a denominator, and combining our two cohorts, the incidence of Schnitzler syndrome in patients with a monoclonal IgM is 1.5%. In this group of 4103 IgM MGUS patients, the kappa to lambda ratio was 67.8% to 32.2% (a ratio of ~2:1). A χ^2 analysis of this distribution compared to the light chain used in our patients with Schnitzler syndrome again suggests significant skewing towards kappa light chain restriction (odds ratio=1.939, 95%CI:1.06, 3.83; *P*=0.04).

Discussion

There is no specific test for Schnitzler syndrome and diagnosis requires a high index of suspicion. The differential diagnosis is broad and includes autoimmune, infectious, neoplastic and idiopathic conditions.[4,5] Diagnostic tests are often used to exclude other conditions that may mimic the syndrome, but once the condition is recognized, the response to anakinra is often gratifying. Unfortunately, chronic urticaria and the presence of a monoclonal protein are both common in the general population. In one study from Olmsted County Minnesota, urticaria has a prevalence of 5.9% in the population.[11] However, the prevalence of chronic urticaria is lower at 0.8%.[12,13] Likewise, MGUS is also common in the general population and its prevalence increases with age.[14,15] Interestingly, Bida *et al.* observed that the prevalence of urticaria in patients with MGUS is *lower* than in the general population (3.3% *vs*. 5.9% for a risk ratio of 0.6; *P*=0.02).[11] The monoclonal protein in MGUS is an IgM isotype in 15-20% of cases.[10,11] During the interval of our current study (1972-2010), 4103 patients with an IgM monoclonal protein were seen at our institution. The kappa to lambda ratio for this cohort was 2:1, while as reported above, we saw considerable skewing towards the use of kappa light chain use in our cohort of patients. One can determine that the likelihood that these two conditions occur in the same patient but are unrelated is low. Our results suggest that the odds ratio for a correlation between an IgM monoclonal protein and chronic urticaria is very high (odds ratio 9801; *P*=0.0001). Therefore, there should be a high index of suspicion when a patient has chronic urticaria and a kappa light chain restricted IgM protein in their serum since the possibility that they have Schnitzler syndrome is significant (and similar to the risk that such a patient will develop multiple myeloma).

Several other points can be raised from the analysis of our cohort. i) Although the risk of progression to a lymphoproliferative disorder is often considered to be high (in the range of 30-45%), in our series this was significantly lower at 8%. A potential explanation could be the tendency for referral and reporting of severe cases while our series could be more representative of the general population. ii) Peripheral neuropathy is quite common in these patients and possibly related to the monoclonal protein since this is well described in patients with an IgM monoclonal protein.[16,17] Our studies suggest that neuropathy can be found more often than previously recognized.[4] iii) Although small monoclonal proteins are frequently identified in patients and generally dismissed as 'MGUS', not all small monoclonal proteins are 'benign'. Small and 'malignant' B-cell or plasma-cell clones exist and their relationship to disease must be recognized since proper therapy can considerably improve patient Quality of Life.[18] iv) Our 4 patients treated with anakinra expand on the growing experience with the use of this agent for Schnitzler syndrome. The response to therapy is rapid and complete. We have also observed rapid relapse if the patient misses any dose of therapy or decides to administer the agent every other day. Such a response is almost diagnostic of the syndrome and we are not aware of any other condition where the response is so rapid and complete. v) Patients with low complement levels generally have another diagnosis rather than Schnitzler syndrome and these patients often do not respond to anakinra. We are aware of at least 2 patients who were tentatively diagnosed with Schnitzler syndrome in the presence of low C3 or C4 and neither of these patients responded to anakinra. On repeat biopsy of the skin, there was clear evidence of vasculitis that is not typical of this syndrome. vi) Since not every patient with chronic urticaria seen at our institution had a monoclonal protein study, it is possible that our results under-estimate the true incidence of Schnitzler syndrome in this population.

In summary, Schnitzler syndrome may be an underdiagnosed clinical syndrome. Patients with chronic urticaria and a concomitant IgMκ monoclonal protein have a reasonable likelihood of having this syndrome, and this diagnosis should be seriously considered in these patients since therapy with anakinra can lead to dramatic responses and improved Quality of Life.

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