A scale for patient-reported symptom assessment for patients with Erdheim-Chester disease

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Key Points

- Collaboration among clinical experts, behavioral research methodologists, and patients can yield valuable symptom-assessment tools.

- Patients with ECD possess widely varied and unappreciated symptomatology.

Erdheim-Chester disease (ECD) is an ultra-rare hematologic neoplasm characterized by somatic mutations of the MAPK pathway and by accumulation of lesional histiocytes within tissues. Clinical phenotypes and sites of disease involvement are heterogenous in ECD, and no tool exists for systematic and comprehensive assessment of ECD symptomatology. We describe a collaborative effort among ECD specialists, patient-reported outcome (PRO) methodologists, and ECD patients to develop the Erdheim-Chester Disease Symptom Scale (ECD-SS): a symptom inventory for clinical ECD care and evaluation of ECD therapies. Methodologically rigorous focus groups led to the identification of 63 ECD symptoms in 6 categories, incorporated into the ECD-SS with respect to both severity and frequency. Among 50 ECD patients participating in a prospective registry study completing the ECD-SS, 46 (92%) reported neurological/psychological symptoms, 29 (58%) reported pain, and at least one-half reported mood symptoms, memory problems, or fatigue. Symptoms were highly frequent or almost constant regardless of their severity. The ECD-SS is a rigorously developed, patient-centered tool that demonstrates the wide and previously unappreciated burden of symptomatology experienced by ECD patients. Further studies will refine the symptom inventory and define its psychometric properties and role in clinical care and investigation in the context of ECD.

Introduction

Erdheim-Chester disease (ECD) is an inflammatory hematologic neoplasm, marked by recurrent somatic mutations in the MAPK pathway whereby histiocytes accumulate in tissues and cause illness.[1] ECD lesions can infiltrate any organ system[2,3] and cause pain, organ dysfunction, and disfigurement from tumoral infiltration. Additionally, clinical disease is mediated by cytokine elevations and perturbations,[2,4,5] causing constitutional symptoms of fever, sweats, and fatigue. Despite the array of symptoms that characterize ECD, there are no standardized disease-specific assessments to measure symptom burden within this heterogeneous population. Patient-reported outcomes (PROs) are data elements directly reported by patients about symptoms and quality of life. There is increasing evidence that rigorous collection and analysis of PROs improves patient-centered care, especially for rare diseases.[6-8] To create an informative PRO tool across the phenotypic spectrum of ECD, both for clinical care and for evaluating ECD therapies in clinical trials, we organized a collaboration among ECD clinicians, PRO methodologists, and ECD patients. Here, we describe the process of establishing the content validity of the Erdheim-Chester Disease Symptom Scale (ECD-SS) using
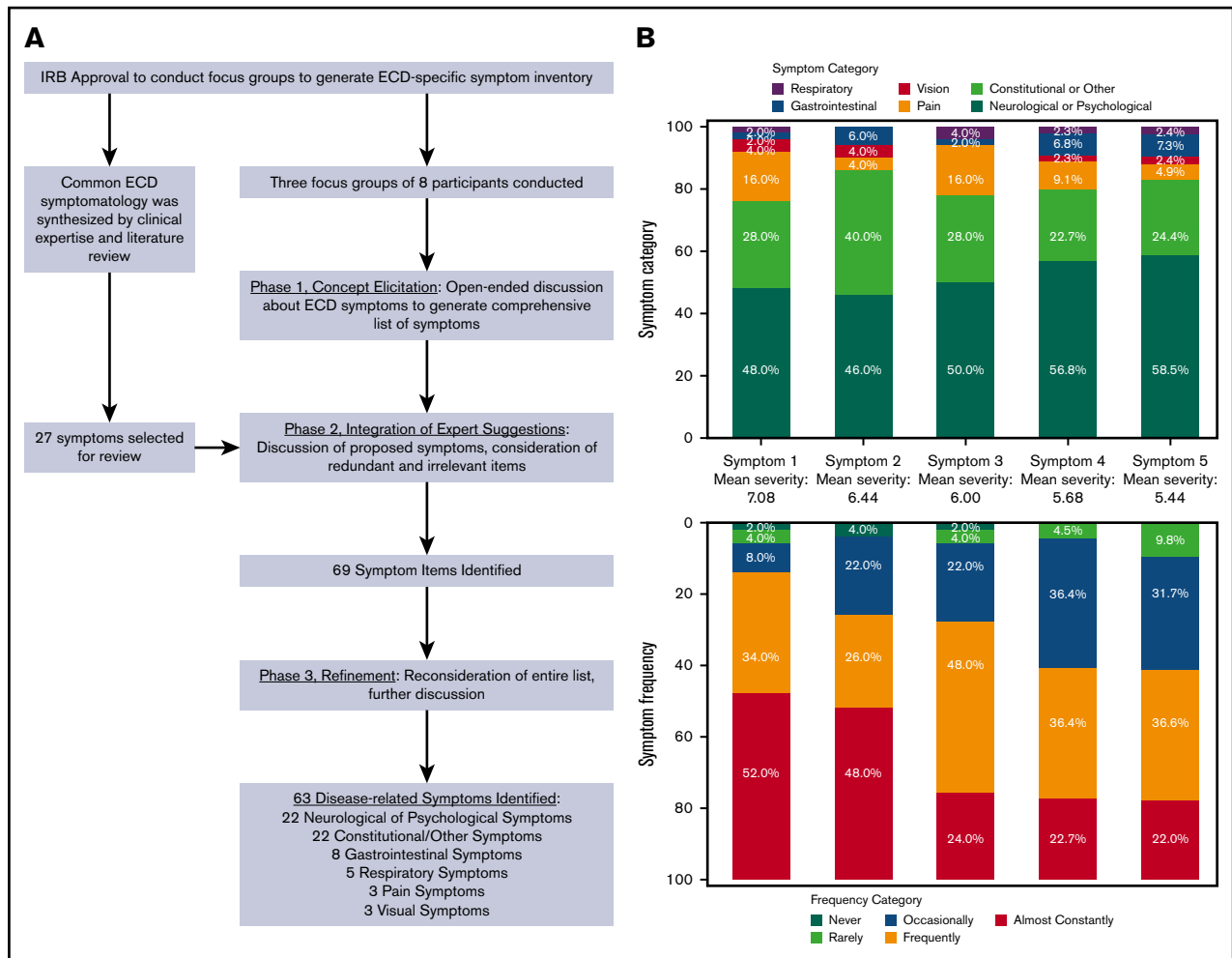
Figure 1. ECD-SS. (A) The collaborative process of generating the ECD-SS symptom inventory. (B) The distributions of symptom categories and frequencies are presented by each level of symptom severity. Mean symptom severity is presented between each stacked bar chart.

state-of-the-art focus-group methodology, and we present the first prospective data on frequency and severity of symptoms in a cohort of ECD patients.

Methods

Institutional review board (IRB) approval was obtained to conduct focus groups and to analyze transcripts of audio-recorded data. The discussions described herein took place at the Patient and Family Gathering hosted by the Erdheim-Chester Disease Global Alliance on 10 October 2015 during the Fourth Annual International ECD Medical Symposium in Houston, TX. Because focus-group data were collected anonymously and without protected health information, the requirement for written informed consent was waived. ECD patients or caregivers could partake in the discussions.

The format (setting, duration), content (wording of questions and prompts), and execution (sequence of discussions, techniques for facilitation) of focus groups was designed by the Patient-Reported Outcomes, Community-Engagement and Language (PRO-CEL) Core at Memorial Sloan Kettering Cancer Center

based on methodological best practices for PRO measure design.[9,10] Focus groups (conducted by E.L.D. and J.J.B.) with 7 to 9 participants each were planned to last 60 to 90 minutes. Focus-group discussions were iterative in their design and execution with 3 phases as follows.

Concept elicitation: phase 1

Facilitators asked open-ended questions about ECD symptoms, allowing participants to describe their experiences fully and without interruption. Participants were also asked their opinions about how ECD symptoms should best be measured. Facilitators interpreted and reflected responses to the group to generate a list of specific symptoms from the discussion.

Integration of expert suggestions: phase 2

Prior to the focus groups, clinicians with expertise in ECD (E.L.D., D.M.H., O.A.-W., F.J.) created a list of symptoms synthesized from ECD literature, guidelines,[11] and clinical experience. This proposed symptom list was presented to participants, who were invited to reflect upon the items for inclusion in or exclusion from the list created in phase 1.

Refinement: phase 3

Participants reviewed and appraised the aggregated list of participant- and clinician-generated symptoms to refine and reconsider the entire inventory. Participants were invited to share further thoughts about the discussion, and, in the process, to further add, remove, or modify symptom items. Aspects of symptomatology (eg, frequency, severity) most relevant to measurement were discussed. At the conclusion of the discussion, there was consensus that all participants' symptoms were represented on the list and that, conversely, there were no extraneous items on the list (ie, applicable to no one in the group). Transcripts of the discussion were subsequently reviewed by the PRO methodologists to develop the ECD-SS.

Pilot data collection and analysis

The ECD-SS was administered to participants in a prospective, IRB-approved ECD registry study (NCT03329274). All patients provided informed consent to the study per the Declaration of Helsinki. Participants completed the ECD-SS via a secure web-based platform implemented frequently in PRO research. Symptom frequency and severity were analyzed descriptively using SAS version 9.4 (Cary, NC).

Results

Focus groups and ECD-SS

Three focus-group discussions were conducted, each with 8 participants. Of the 24 participants, 16 were ECD patients and 8 were caregivers. Each focus-group discussion was 45 to 60 minutes in length.

The process of generating the ECD-SS symptom inventory is schematized in Figure 1. Six categories of symptoms were identified: neurologic or psychological, gastrointestinal, pain-related, vision-related, respiratory or breathing, and a broad category of constitutional and other symptoms. Following phase 2 of the discussions, 69 symptoms were identified. Six symptoms were removed during refinement, yielding 63 ECD symptoms.

The scale was designed to measure both symptom frequency and severity. ECD-SS respondents check off all experienced ECD symptoms and rank the severity of their 5 most severe symptoms. Each symptom is rated on a numeric severity scale from 0 to 10. Frequency is rated for each symptom on a 5-point Likert scale (never, rarely, occasionally, frequently, almost constantly).

ECD symptoms

We present ECD-SS data from 50 ECD patients, a separate cohort from focus-group participants; patient characteristics and reported symptoms are summarized in Table 1. Sixty-two of 63 symptoms in the inventory were endorsed by a least 1 participant. Neurologic or psychologic symptoms were reported by 92%, with 50% or more of participants reporting depression or sadness, stress/anxiety, or memory problems, and 72% reporting fatigue or sleepiness. Aching bones or joints was reported by 56%, generalized pain by 36%, and aching muscles by 28%. Symptoms related to balance and dexterity, as well as those related to cognition were frequently reported. The distribution of symptom categories and their frequency, according to symptom severity, is presented in Figure 1. For the most severe symptom reported, the mean severity was 7.08 (standard deviation, 2.02). This most severe symptom reported was neurologic/psychological for 24 (48%) of participants, constitutional/other for 14 (28%),

Table 1. Clinical characteristics and prevalence of symptoms as reported on the ECD-SS

Characteristic	N*	%*
Age, y	56.1 (median)	18-77 (range)
Sex		
Male	28	56
Female	21	42
Unknown	1	2
Race		
White	46	92
African American	1	2
Asian	2	4
Unknown	1	2
Self-reported disease locations		
Bone	36	72
Skin	8	16
Brain	23	46
Lungs	8	16
Heart	14	28
Kidneys	23	46
Eyes	16	32
Spine	9	18
Treatment at time of completing ECD-SS		
Targeted therapy†	27	54
Conventional therapy‡	9	18
Targeted and conventional therapy	1	2
No current treatment	9	18
Unknown	4	8
Neurologic or psychological symptoms		
Memory problems (forgetfulness, repeating questions or statements)	26	52
Depression or sadness	25	50
Stress/anxiety	25	50
Trouble with balance or walking	25	50
Short-tempered	21	42
Discouragement	19	38
Weakness of the arms or legs	18	36
Mood swings	17	34
Trouble with dexterity/coordination	17	34
Difficulty concentrating or paying attention	17	34
Numbness or tingling in hands or feet	15	30
Ringing in the ears (tinnitus)	14	28
Speech difficulties	13	26
Choking (while eating or drinking)	11	22
Difficulty swallowing	11	22
Dizziness	11	22
Head rush or light headedness or spinning sensation (vertigo)	10	20

*Columns 2 and 3 represent number and percent of patients, respectively, except as noted in row 1.

†Vemurafenib, dabrafenib, cobimetinib, trametinib, or dual BRAF/MEK therapy.

‡Corticosteroids, interferon, anakinra, tocilizumab, methotrexate.

Table 1. (continued)

Characteristic	N*	%*
Headache	8	16
Inappropriate crying	3	6
Inappropriate behavior	3	6
Personality changes	2	4
Inappropriate laughter	1	2
Constitutional or other symptoms		
Fatigue or sleepiness	36	72
Decreased sexual interest	16	32
Frequent or excessive urination	15	30
Insomnia or difficulty sleeping	14	28
Sudden urge to urinate	13	26
Night sweats	12	24
Inability to sleep due to pain	11	22
Itchy skin	11	22
Rash or skin problems	11	22
Frequent napping	10	20
Swelling of the arms or legs (edema)	10	20
Inability to drive	8	16
Hot flashes	7	14
Inability to sleep lying down	7	14
Problems tasting food	4	8
Changes in smell	3	6
Pounding or racing heart (palpitations)	3	6
Other problem that was not listed or I do not have any symptoms.	3	6
Fever	2	4
Hyperhidrosis (excessive sweating)	2	4
Urinary incontinence	2	4
Urinary tract pain	1	2
Gastrointestinal symptoms		
Dry mouth	15	30
Diarrhea	13	26
Abdominal pain	10	20
Decreased appetite	7	14
Nausea	7	14
Dental problems	3	6
Ulcers or other stomach problems	1	2
Vomiting	0	0
Pain		
Aching bones or joints	28	56
Pain	18	36
Aching muscles	14	28
Visual symptoms		
Blurred vision	11	22
Changes in vision	6	12
Double vision	5	10
Respiratory symptoms		
Cough	9	18

Table 1. (continued)

Characteristic	N*	%*
Shortness of breath (in general)	7	14
Trouble breathing at night	3	6
Trouble breathing/shortness of breath (in general)	1	2
Hypoxia (air hunger from low oxygen)	1	2
Most common in patients on no treatment (N = 9)		
Stress/anxiety	8	89
Fatigue or sleepiness	7	78
Memory problems	7	78
Depression or sadness	6	67
Aching bones or joints	6	67
Most common in patients on conventional therapy (N = 9)		
Short-tempered	5	56
Difficulty concentrating or paying attention	5	56
Aching bones or joints	5	56
Pain	5	56
Fatigue or sleepiness	5	56
Most common in patients on targeted therapy (N = 27)		
Fatigue or sleepiness	19	70
Depression or sadness	13	48
Trouble with balance or walking	13	48
Memory problems	13	48
Aching bones or joints	13	48

*Columns 2 and 3 represent number and percent of patients, respectively, except as noted in row 1.

†Vemurafenib, dabrafenib, cobimetinib, trametinib, or dual BRAF/MEK therapy.

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gastrointestinal for 1 (2%), pain for 8 (16%), visual for 2 (4%), and respiratory for 1 (2%). Symptoms were reported to be highly frequent, irrespective of severity: the most severe symptom was reported to be either frequent or almost constant for 43 participants (86%) and was frequent or almost constant for 29 (58%) for the least severe symptom. Of note, 37 participants (74%) were undergoing active treatment at the time of completing the ECD-SS.

Discussion

We describe here the collaborative and patient-centered methodologic process of developing a comprehensive symptom inventory for ECD. The disease symptomatology captured from the ECD-SS suggests an extensive burden of symptoms in ECD patients, exceeding that which has been described in the literature.[11-14] All symptoms on the inventory except for 1 were endorsed by at least 1 of the 50 ECD patients completing the assessment, supporting the content validity of the ECD-SS items as resonant with real-world patient experience. These pilot data further illustrated that frequent symptoms such as impaired cognition, psychological distress, pain, and constitutional symptoms are those that do not have a correlate on imaging scans. Moreover, these symptoms are present in a largely treated population, suggesting inadequate supportive management even in the setting of controlled disease. Therefore, these symptoms are not measured, or evaluated with respect to therapeutic response, by traditional radiologic assessments. This highlights an important

gap, and opportunity for meaningful improvement, within the clinical assessment of ECD patients. A limitation of this kind of assessment, particularly when performed cross-sectionally, is that disease-related symptoms are not distinguished from treatment side effects. Further study of the ECD-SS will involve investigation of its psychometric properties, including methods such as internal consistency, factor analysis, and principal components analysis, which could provide quantitative insights into reconsidering the symptom categories and refining the inventory by removing redundant items. Other avenues of future inquiry will involve methods of composite scoring and of changes in symptom scores across time points. Continued implementation and evaluation of the ECD-SS within clinical care and investigational studies will help to define its role in comprehensive ECD assessment.

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Authorship

Contribution: E.L.D., J.J.B., T.M.A., F.J., K.B., and J.C. collected the data; E.L.D., A.S.R., J.J.B., E.S., A.J.A., R.R., K.B., J.C., J.J.M., T.M.A., and K.S.P. analyzed and interpreted the data; E.L.D., A.S.R., J.J.B., E.S., A.J.A., D.M.H., O.A.-W., R.R., F.J., K.B., J.C., J.J.M., T.M.A., and K.S.P. wrote the manuscript; and all authors approved the final manuscript.

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