

Challenges and positive impact of rare cancer caregiving: A mixed-methods study of caregivers of patients with Erdheim-Chester disease and other histiocytic neoplasms

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Summary

Background The importance of deriving benefit and meaning has been identified among cancer caregivers, but this has yet to be examined in the context of rare cancers. We sought to characterize unmet needs and experiences of caregivers of patients with Erdheim-Chester disease (ECD) and other histiocytic neoplasms (HN) and to identify factors associated with finding benefit and meaning-making in providing care for patients with rare cancers.

Methods Caregivers of patients with ECD and other HN completed quantitative surveys. Linear univariable regression modeling examined associations between unmet needs, social and family support, and intolerance of uncertainty with benefit finding and meaning-making. A subset participated in qualitative interviews assessing experiences of rare cancer caregiving that were analyzed with applied thematic analysis (NCT039900428).

Findings Of caregivers ($N = 92$, $M = 54$ years old, 68% female) of patients with ECD (75%) and other HN (25%), 78% reported moderately or severely unmet support needs, most frequently informational (58%) and psychological/emotional (66%) needs. Caregivers with unmet informational, psychological/emotional, and social support needs, difficulty tolerating uncertainty, a longer duration of the patient's illness, lower social support, more family conflict, and higher anxiety and depression symptoms demonstrated less benefit finding and meaning-making ($ps < .05$). Qualitative interviews ($N = 19$) underscored information and support needs and the capacity to derive meaning from caregiving.

Interpretation Rare cancer caregivers report numerous unmet information and support needs, needs that arise from disease rarity itself and which are associated with diminished capacity for deriving benefit and meaning from caregiving. Findings highlight targets for interventions to improve support for caregivers with HN and other rare cancers.

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Research in context

Evidence before this study

The existing literature suggests that caregivers providing support to patients with cancer endure tremendous burden and unmet needs, and at the same time have the capacity to derive benefit and meaning from the caregiving experience. The positive and negative elements of providing care specifically in the context of rare cancers, however, has been minimally investigated. A search in PubMed for articles published from inception to 1 Aug 2022 using the terms (Rare OR Orphan) AND Cancer AND (Caregiver OR Carer) yielded 180 articles. Ten articles were relevant to caregivers of rare cancers; 4 were qualitative, 2 were quantitative survey-based, 2 were topic reviews, one was a pilot mixed-methods study, and one evaluated an educational program. None of these analyzed caregiver and patient characteristics associated with positive elements of caregiving, nor did any seek to identify opportunities for intervention to enhance meaning-making and benefit-finding in the context of rare cancer caregiving.

Added value of this study

Our study assessed 92 caregivers of patients with histiocytic neoplasms with mixed methodology. This study identified highly frequent unmet needs for supportive care in this caregiver population, and furthermore we identified that these unmet needs, such as for informational and social support, are associated with diminished benefit-finding and meaning-making. Furthermore, qualitative data shed insight onto these unmet need as emanating from the challenges of providing care for a patient with a rare cancer. Our study provides targets for intervention to improve psychosocial outcomes for these caregivers. While individual rare cancers are rare, rare cancers in aggregate comprise 20% of all cancers, and therefore these results are valuable for a substantial proportion of cancer caregivers.

Implications of all the available evidence

The psychological and physical health toll of cancer caregiving is potentially debilitating, and our findings suggest these challenges may be magnified among rare cancer caregivers owing to scarcity of information and limited social support. Our study contributes the dimension of positive changes (i.e., benefit-finding and meaning-making) stemming from cancer caregiving. Rare cancer caregivers' informational and support needs are uniquely unmet and, and future studies should examine interventions aimed to target them most effectively and efficiently to reduce distress and bolster benefit-finding and meaning-making.

Introduction

The histiocytic neoplasms (HN) including Erdheim-Chester Disease (ECD) and Langerhans cell histiocytosis

(LCH) are rare hematologic cancers characterized by recurrent activating mutations in the mitogen activated protein kinase (MAPK) pathway.^{1–4} ECD is a highly rare neoplasm in adults with only ~1500 cases reported in the literature.⁵ HN can affect multiple organ systems resulting in protean manifestations, varied clinical presentations, and delayed diagnosis. The current era of molecular therapies has afforded patients with ECD and other HN effective treatment options that have diminished mortality from these disorders. Increased survivorship has allowed for investigation of psychosocial outcomes, symptomatology, and caregiver experiences.^{6–8}

A patient navigating the diagnosis and management of any cancer typically relies on the involvement of a caregiver, or unpaid support person.⁹ Caregivers assist in obtaining information about the patient's disease, help the patient plan and undergo treatment, provide support with activities of daily living, and in this process require variable degrees of dedicated support for themselves. The demands of caregiving are linked to immediate and long-term mental and physical health sequelae.^{9–11} For many, caregiving disrupts existing roles and responsibilities, and coupled with the existential threat of the patient's illness, results in significant distress. Diminished wellbeing among caregivers, in turn, can contribute to worsened mood¹² and health outcomes¹³ among patients. Despite these challenges, caregivers may derive positive value from their experience (i.e., benefit finding)^{14–17} and/or connect to a sense of meaning and purpose (i.e., meaning-making).^{18,19} Such positive experiences have been found to promote psychological adjustment and buffer the suffering and negative health impact of caregiving.

In the context of rare cancers—about which information and expertise are often scarce—the constellation of experiences, information and support needs, and capacity for benefit finding and meaning-making is not well understood. The rarity of ECD and HN, coupled with the limited available information about treatment options, may render it especially challenging for caregivers to obtain adequate support. We previously conducted a pilot study that suggested substantial impact of ECD caregiving, including frequent disruptions in family roles and responsibilities, financial burden, unmet needs, and elevated anxiety.⁸ Supportive care needs and psychosocial outcomes, and their association with caregivers' finding benefit and meaning-making in their experience have yet to be comprehensively characterized in these rare diseases.

To develop targeted and tailored interventions to promote wellbeing among caregivers of patients with rare cancers, the unique needs of this group of caregivers require greater understanding. We conducted an embedded mixed-methods study²⁰ to identify the frequency and nature of unmet needs in caregivers of patients with ECD and other HN and to examine individuals' lived experiences in providing care and support.

We hypothesized that unmet needs and psychosocial factors emanating from the rarity of HN (i.e., difficulty assessing information, finding expertise, and social support, intolerance of uncertainty, anxiety and depression) would be negatively associated with the experience of benefit finding and meaning-making in caregiving.

Methods

Ethics statement

Recruitment occurred between March 7, 2018 and January 31, 2021. The study was reviewed and approved by the MSK Institutional Review Board (IRB #19-213) and it was registered with ClinicalTrials.gov (NCT 03990428). All participants signed an informed consent form. The study was conducted in keeping with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.²¹

Participants

Caregiver participants were recruited from the Departments of Neurology and Medicine at Memorial Sloan Kettering Cancer Center (MSK) or referred from the ECD Global Alliance or Histiocytosis Association (patient advocacy group dedicated to ECD and histiocytosis, respectively). Inclusion criteria for the caregivers were self-identifying as a family member or friend who provides unpaid support for a patient with ECD or another histiocytosis (i.e., Langerhans cell histiocytosis or Rosai-Dorfman disease), proficiency to complete study assessments in English, and age 18 or over. The diagnosis of the patient's histiocytosis was verified by Principal Investigator (E.L.D.) review of medical records and by formal pathology review of biopsy material. Interested and eligible participants provided written or electronic informed consent.

Survey procedures and data elements

Participants completed a one-time battery of questionnaires on a secure REDCap server which took approximately 45 minutes. The battery included a socio-demographic questionnaire, as well as multiple well-validated instruments which have demonstrated reliability and validity in large samples and in cancer populations. The outcomes of primary interest for this study were benefit finding and meaning-making. Benefit finding refers to the ability to identify positive aspects of and experience growth from adversity.¹⁵ Meaning-making refers to the ability to find meaning in life while experiencing adversity.^{17,19} These constructs were measured with the Benefit Finding Scale (BFS)²² and Attitudes Towards Caregiving Scale (ATCS),²³ respectively. The 17-item BFS asks caregivers to rate, using a 5-point Likert-type format, the extent to which providing care has resulted in benefits with items such as “[their cancer

experience has] contributed to my overall emotional and spiritual growth,” and “led me to deal better with stress and problems.” The 43-item ATCS asks caregivers to respond, with a 5-point Likert-type format, the extent to which they find meaning through caregiving. Items include “caring for my loved one gives my life a purpose and a sense of meaning,” and “each year, regardless of the quality, is a blessing.”

The battery also included measures of caregiver supportive care needs (Supportive Care Needs Survey—Partners & Caregivers: SCNS-PC),²⁴ perceived social support (Duke-UNC Functional Social Support Questionnaire: FSSQ),²⁵ family communication (The Cancer Communication Assessment Tool for Families: CCAT-F),²⁶ anxiety and depression (Hospital Anxiety and Depression Scale: HADS)²⁷ and intolerance of uncertainty (Intolerance of Uncertainty Scale, 12-item version: IUS-12)²⁸ Intolerance of Uncertainty included subscales of inhibitory anxiety (i.e., avoidance behaviors) and prospective anxiety (i.e., concern about the future) and a total intolerance of uncertainty score.²⁸ Clinical variables (age, sex, duration of undiagnosed illness from symptom onset to confirmed diagnosis, and duration of total illness from symptom onset to study participation) for the ECD/HN patient for whom the participant provided care was collected if available.

Semi-structured interview

A subsample of caregivers was selected to participate in a one-time semi-structured qualitative interview. Purposeful sampling²⁹ was used to obtain a sub-sample for the qualitative interviews representative in terms of caregiver demographics such as age, sex, race, ethnicity, as well as the patient's clinical symptom burden. Interviews were conducted at the time of enrollment by K.A. L. and were 45–60 min long. They were conducted over the phone and were audio-recorded and transcribed verbatim. We estimated that approximately 20 interviews would be sufficient to achieve thematic saturation, or the point at which relevant topics are fully explored, based on previous qualitative studies conducted among a single sample.³⁰ The semi-structured interview guide was developed by the Patient Reported Outcomes and Community Engagement and Language (PRO-CEL) Core and was adapted to elicit themes related to rare cancer caregiving that arose in our pilot.⁸ The interview explored the following topics: 1) caregiver prognostic understanding and information needs, 2) caregiving responsibilities, 3) impact of caregiving on quality of life, 4) access to psychosocial support.

Statistical analysis

Quantitative survey data. Descriptive statistics including frequencies, means, and standard deviations were

used to characterize the cohort and summarize caregiver assessment responses. Needs were considered unmet if they were rated as moderately or highly unmet. Clopper-Pearson exact 95% confidence intervals were calculated for unmet needs. Univariable linear regression modeling was performed to associate variables of interest (from the caregiver participants and corresponding patients) with ATCS score and BFS score separately. Multivariable modeling was not performed due to multicollinearity of variables. If any item of the ATCS or BFS was missing, the specific assessment was not scored for that caregiver. The mechanism for missingness was assumed to be unrelated to ATCS and BFS. Tests were two-sided with an alpha level of statistical significance <0.05. Participants were compared by recruitment site on continuous variables of interest using the t-test or Wilcoxon two sample test depending on normality of the data and compared on categorical variables of interest using Fisher's Exact tests. Normality of data was assessed both visually with histograms and formally with the Shapiro-Wilk test for normality. Analyses were performed in SAS v9.4 (The SAS Institute, Cary, NC).

Qualitative interview data. Transcripts were analyzed using applied thematic analysis, a rigorous inductively-driven approach to identify and examine themes from textual data, commonly used in mixed-methods analyses.³¹ Two coders (K.A.L., A.S.) first coded a randomly-selected sample of transcripts (*n* = 5) using an initial list of codes derived from the domains of the interview guide. The coding team met to refine code names and definitions and incorporate inductively derived codes based on novel concepts that emerged from the data, developing a consensus codebook. The team then independently coded the remaining transcripts (*n* = 14), meeting regularly to achieve consensus on emerging concepts and to resolve discrepancies. Once all data were coded, the team grouped the codes into conceptual categories and completed a secondary review of statements grouped into each category to identify primary themes. The final phase of analysis involved a collaborative discussion with the wider study team to identify and describe the most prominent and salient themes and their relation to the quantitative data. Transcripts were coded using the software NVivo Pro version 12.0 (QSR International).

Role of the funding source

The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The corresponding author (ELD) had full access to all data in the study and all authors had responsibility in submitting the paper for publication.

Results

A total of 101 caregivers enrolled in the study, and 92 (91%) provided complete ATCS or BFS data for the current analyses. Eight caregivers were missing both ATCS and BFS scores and one caregiver each was missing an ATCS score or BFS score so that nine caregivers were missing ATCS scores and nine caregivers were missing BFS scores. Participant characteristics are presented in Table 1. The 92 caregivers were mostly female (68%), White (74%), and middle aged (*M* = 54, *r*: 20–82). Caregivers were largely the partner/spouse of the patient (70%). Most had a college or professional degree (74%).

		M	Range
Age		54	20–82
Patient duration undiagnosed illness (years)		2.25	0.00–10.08
Patient duration total illness (years)		5.96	0.08–22.03
		N	%
Sex	Male	28	30
	Female	63	68
	Other	1	1
Race	White	73	79
	Asian/Pacific Islander	9	10
	African American/ Black	3	3
	American Indian/ Aleut/Eskimo	1	1
	Not reported	6	7
Ethnicity	Hispanic/Latinx	13	14
	Non-Hispanic/Latinx	79	86
Relationship to patient	Parent	8	9
	Spouse/Partner	64	70
	Adult Child	8	9
	Sibling	4	4
Marital Status	Friend/ Other	8	9
	Married/Partnered	77	84
	Single, never married	8	9
	Divorced	5	5
	Widowed	2	2
Education	High school diploma/GED	10	11
	Vocational school/ Some college	14	15
	College degree	34	37
Income	Professional or graduate school	34	37
	< \$40,000	10	11
	\$40,000–<\$75,000	22	24
	≥\$75,000	54	59
Employment status	Prefer not to answer	6	7
	Paid full-time employed	35	38
	Paid part-time employed	7	8
	Self-employed	7	8
	Retired/disabled	27	29
Patient Diagnosis	Unemployed	15	16
	Not reported	1	1
	Erdheim-Chester Disease	69	75
	Langerhans Cell Histiocytosis	13	14
	Rosai-Dorfman Disease	6	7
	Juvenile Xanthogranuloma	1	1
Site	Other	3	3
	Memorial Sloan Kettering	70	76
	ECD Global Alliance/ Histiocytosis Association	22	24

Table 1: Caregiver sociodemographic characteristics (N = 92). Abbreviations: N=Number; M=Mean; GED=General Educational Development Test.

	N (%)	M (SD)
Caregiver Supportive Care Needs		..
Met health care service needs	39 (42)	..
Unmet health care service needs	51 (55)	..
Unknown health care service needs	2 (2)	..
Met psychological & emotional needs	30 (33)	..
Unmet psychological & emotional needs	61 (66)	..
Unknown psychological & emotional needs	1 (1)	..
Met work & social needs	51 (55)	..
Unmet work & social needs	40 (43)	..
Unknown work & social needs	1 (1)	..
Met informational needs	38 (41)	..
Unmet informational needs	53 (58)	..
Unknown informational needs	1 (1)	..
Met total needs	19 (21)	..
Unmet total needs	72 (78)	..
Unknown total needs	1 (1)	..
At least 5 unmet needs	51 (55)	..
>5 unmet needs	49 (53)	..
At least 10 unmet needs	45 (49)	..
>10 unmet needs	44 (48)	..
Social Support (range: 14–70)	..	52.8 (13.9)
Family Communication (range: 6–36)	..	14.8 (5.3)
Intolerance of Uncertainty: Total (range: 12–52)	..	26.1 (8.4)
Intolerance of Uncertainty: Prospective Anxiety (range: 7–31)	..	17.2 (5.7)
Intolerance of Uncertainty: Inhibitory Anxiety (range: 5–21)	..	8.9 (3.3)
Meaning of Caregiving (range: 79–177)	..	133.4 (21.5)
Benefit Finding (range: 18–85)	..	59.6 (14.0)

Table 2: Caregiver psychosocial characteristics (N=92).

Abbreviations: N=Number, M=Mean, SD=Standard Deviation.

Note: Number of caregiver unmet supportive care needs = count of moderate to high needs⁴⁸; Prospective anxiety refers to anxiety in anticipation of future uncertainty; Inhibitory anxiety refers to inaction in the face of uncertainty²⁶

Patients were primarily diagnosed with ECD (75%), went an average of 2.25 (SD = 2.78) years with undiagnosed illness (*i.e.*, time elapsed between start of clinical symptoms and confirmed diagnosis) and had an average duration of total illness of 5.96 (SD = 4.90) years. Caregivers recruited from MSK ($n = 70$) and those recruited from the ECD Global Alliance or Histiocytosis Association ($n = 22$) were similar in terms of individual characteristics ($ps > .12$). However, caregivers recruited outside of MSK were more likely to be taking care of a patient with ECD ($p = .03$) and with a longer duration of undiagnosed and total illness ($ps < .01$).

Quantitative findings

Caregiver unmet needs and psychosocial factors (*i.e.*, social support, family communication, intolerance of uncertainty, meaning-making and benefit finding) are reported in Table 2. Most caregivers (78%) reported any unmet needs. Regarding specific unmet needs, 66% (95% CI: 55.7–75.8) reported unmet psychological and emotional needs, 58% (95% CI: 46.9–67.9) reported unmet informational needs, 43% (95% CI: 33.2–54.2) reported unmet work and social unmet needs, and 55% (95% CI: 44.7–65.8) of caregivers reported unmet health care service needs. 55% (95% CI: 38.3–59.6) reported five or more unmet needs and 49% reported ten or more unmet needs.

Greater levels of social support ($B = 0.33$, $p < 0.01$) and less family conflict ($B = -0.93$, $p < 0.001$) were associated with higher levels of benefit finding (Table 3). That is, for each additional point increment for the family conflict assessment scale, there was almost a point decrease on the benefit finding scale. Younger caregiver age ($B = -0.039$, $p = 0.03$), lower level of education attained ($B = -14.6$, $p < 0.01$), having fewer unmet health service needs ($B = -12.2$, $p < 0.01$), psychological and emotional needs ($B = -13.42$, $p < 0.01$), work and social needs ($B = -15.57$, $p < 0.001$), and informational needs ($B = -9.75$, $p = 0.03$) were associated with greater meaning-making. Higher social support ($B = 0.68$, $p < 0.0001$), less family conflict ($B = -1.11$, $p < 0.01$), less prospective anxiety ($B = -0.91$, $p = 0.02$), less inhibitory anxiety ($B = -1.80$, $p < 0.01$), less overall illness uncertainty ($B = -0.70$, $p < 0.01$), higher levels of anxiety ($B = -1.80$, $p < 0.01$) and depression ($B = -2.95$, $p < 0.01$) and shorter total duration of total illness were associated with higher levels of meaning-making ($B = -1.69$, $p < 0.01$) (Table 4).

Qualitative findings

Thematic saturation was achieved after 19 interviews. Applied thematic analysis identified and three major themes related to unmet needs and positive impact of caregiving: 1) caregiver burden, 2) information and support needs, and 3) positive coping, each with 3–4 sub-themes. We describe here the themes concerning unmet needs and the positive impact of caregiving as they relate to the rarity of HN. Representative participant statements are included in Table 5.

Unmet needs. Caregivers described unmet information and support needs related to their loved one's diagnosis. Participants noted the scarcity of information about histiocytosis available and accessible to them, specifically treatment and prognosis, which was attributed to its rarity. Most participants described a long period of undiagnosed illness, a major source of frustration, fear and distress. The unique lack of information about these

Variable	UnStd B	95% CI	p
Age	-0.21	-0.44, 0.02	0.07
Sex			
Male	Ref		
Female	4.31	-2.07, 10.68	0.18
Other	-13.74	-41.96, 14.48	0.4
Education			
Less than college	Ref		
College or more	-4.83	-11.42, 1.77	0.15
Relationship to patient			
Spouse/Partner	Ref		
Child	0.97	-9.67, 11.61	0.86
Parent	-0.78	-11.42, 9.86	0.88
Other	-1.69	-10.62, 7.23	0.71
Supportive care needs			
Health care service			
Met	Ref		
Unmet	-4.55	-10.47, 1.37	0.13
Psychological and emotional			
Met	Ref		
Unmet	-4.92	-11.14, 1.30	0.12
Work/Social			
Met	Ref		
Unmet	-5.17	-11.07, 0.72	0.08
Informational			
Met	Ref		
Unmet	-3.33	-9.31, 2.65	0.27
Total needs			
Met	Ref		
Unmet	-3.61	-10.85, 3.64	0.33
Social Support	0.33	0.13, 0.53	<0.01
Family Conflict	-0.93	-1.46, -0.4	<0.001
IUS: Prospective Anxiety Subscale	0.34	-0.19, 0.86	0.20
IUS: Inhibitory Anxiety Subscale	0.28	-0.62, 1.18	0.54
IUS: Total score	0.20	-0.16, 0.55	0.27
Duration of undiagnosed illness	-1.01	-2.17, 0.15	0.09
Duration of illness	-0.31	-1.00, 0.38	0.37
HADS: Anxiety Subscale	0.09	-0.59, 0.77	0.79
HADS: Depression Subscale	-0.74	-1.45, -0.03	0.04

Table 3: Associations of caregiver sociodemographic and psychosocial factors, unmet needs with benefit finding (N=91).

Abbreviations: N=Number; UnStd B=Unstandardized Beta Parameter Estimate; CI=Confidence Interval; IUS=Intolerance of Uncertainty Scale; HADS=Hospital Anxiety and Depression Scale.
Note: There was one caregiver with unknown Supportive Care Needs.

Variable	UnStd B	95% CI	p
Age	-0.39	-0.75, -0.04	0.03
Sex			
Male	Ref		
Female	-2.06	-11.88, 7.76	0.68
Other	-16.96	-60.86, 26.93	0.44
Education			
Less than college	Ref		
College or more	-14.60	-24.37, -4.83	<0.01
Relationship to patient			
Spouse/Partner	Ref		
Child	2.20	-14.00, 18.41	0.79
Parent	-2.17	-18.38, 14.04	0.79
Other	-7.66	-21.77, 6.45	0.28
Supportive care needs ^b			
Health care service			
Met	Ref		
Unmet	-12.2	-20.94, -3.46	<0.01
Psychological and emotional			
Met	Ref		
Unmet	13.42	-22.59, -4.24	<0.01
Work/Social			
Met	Ref		
Unmet	-15.57	-24.05, -7.08	<0.001
Informational			
Met	Ref		
Unmet	-9.75	-18.67, -0.83	0.03
Total needs			
Met	Ref		
Unmet	-12.23	-23.03, -1.43	0.03
Social Support	0.68	0.38, 0.98	<0.0001
Family Conflict	-1.11	-1.93, -0.29	<0.1
IUS: Prospective Anxiety Subscale	-0.91	-1.69, -0.14	0.02
IUS: Inhibitory Anxiety Subscale	-1.80	-3.11, -0.48	<0.1
IUS: Total score	-0.70	-1.22, -0.17	<0.1
Duration of undiagnosed illness	-1.74	-3.60, 0.12	0.07
Duration of illness	-1.69	-2.71, -0.68	<0.1
HADS: Anxiety Subscale	-1.80	-2.77, -0.83	<0.1
HADS: Depression Subscale	-2.95	-3.89, -2.03	<0.1

Table 4: Associations of caregiver sociodemographic and psychosocial factors, unmet needs with meaning-making (N=91).

Abbreviations: N=Number; UnStd B=Unstandardized Beta Parameter Estimate; CI=Confidence Interval; IUS=Intolerance of Uncertainty Scale; HADS=Hospital Anxiety and Depression Scale.
Note: There was one caregiver with unknown Supportive Care Needs.

diseases, as compared to common chronic diseases, was highlighted as a challenge. Many participants described the constant worry over whether a loved one’s symptom was a “typical” part of HN disease progression, or cause for greater concern. Caregivers reported that the information they found on the Internet was often outdated and reflected lack of medical understanding of the rare disease, creating uncertainty and confusion about what to expect in terms of their future caregiving. Patient experiences and perspectives available on the Internet and social media were predominantly negative or pessimistic, stoking feelings of fear and anxiety about the future.

Caregivers also expressed an unmet need for support in managing the psychological and emotional demands of caregiving. This included broader societal recognition

of the experience of caregivers and opportunities to connect with other caregivers of patients with HN. Caregivers described frustration at feeling that they needed to constantly educate others in their social circle about their loved one’s condition, and desired resources for discussing HN with friends and family. They also emphasized the need to receive support from individuals, not limited to the primary medical team, helping them to navigate the illness and manage expectations. These could include social workers, psychologists, or peer support.

Positive impact. Caregivers reported experiences reflective of *benefit finding* and *meaning-making* in qualitative interviews. For example, one subtheme emerged around making positive appraisals. Caregivers

Caregiver Needs	
Information Needs	<p>“...if you have something like diabetes, there’s a ton of literature out there. With Erdheim Chester a lot, even the literature out there is somewhat, pretty much descriptive of symptoms but not a whole lot is out there as far as, you know treatment or prognosis, you know. There’s a lot of ifs, ands, maybes, it could be, without anything definitive.”</p> <p>“And then once we actually got the final diagnosis ECD, I was relieved that they knew what it was, but as soon as I started reading about it, it was terrifying. Because when you first go research ECD there’s not a lot of good news on the Internet. And it’s not necessarily accurate; I know that now. A lot of the information that’s out there is from ten years ago you had six months to live once you were diagnosed, and that’s the kind of stuff I would see. And so, that was extremely terrifying”</p> <p>“Basically it’s been more of an online search because most doctors don’t know - you know haven’t been able - it’s been a quandary to them as well.”</p> <p>And I say this to people that I can cope with just about anything when I know what I’m dealing with. But not knowing what I was dealing with, with the anxiety of that and then the - just being upset watching. It was like the symptom-of-the-month and just watching my husband tumble from somebody that used to be a very, very active person down to somebody that, you know doesn’t have the energy to walk 100 yards was very, very upsetting”</p>
Support Needs	<p>“[I] wish that for people like myself who have to do this, I just wish they were - that our society be more empathetic and try to offer more support for people going - who are caregivers to have more support for them. Because it is extraordinarily difficult and stressful. But it does seem to be in the offering. That’s what I would say, that the people really need to understand that caregivers really need more support than they are currently getting. Because it’s extraordinarily difficult and the emotional toll on them is palpable.”</p> <p>“[I need] somebody that will like talk to me more about what’s going on or you know what the person is going through. Because honestly I never - beside the doctor like I never had anybody else talk to me about that. You know about getting me support on or giving me anything - because they don’t, you know not many people know about that. So there’s not much to say, really.”</p> <p>“I don’t have anybody I can discuss this with because there isn’t anybody that understands what I’m talking about. The doctors are great, don’t get me wrong. But they really don’t know what this is like on a day-by-day basis. They have no idea.”</p>
Positive Impact of Caregiving	
Positive appraisals	<p>“You realize it’s either going to be 2 things. You’re going to either just live each day and enjoy yourself or you crawl up in a ball and you don’t live. That was not an option for us. So we, I said, you know, I have 4 kids. They’re going to have a normal life and we’re just going to be very truthful with them. So that’s it.”</p> <p>“You know, it’s something good will come out of this. That’s how I - I always try to keep that positive outlook, something good will come out of this. I don’t know what, it’ll come, something will happen. I don’t know [...] wouldn’t you want somebody else to benefit from the fact that you had [this experience] whatever you went through?”</p>
Motivation	<p>“So me, you know, but I wanted to know. And it spurred in me the absolute drive to find out everything I could about this. And to see what and how I could process or make his life a little bit easier or doable at least”</p> <p>“I think I’ve been given opportunity to be stronger in ways that I didn’t know I necessarily had. I’ve had to really understand medical information a lot more, be able to explain medical situations in ways that I didn’t think I would have to. So, I just think that that all has been – it’s taken to a different level. Instead of having to - - I’m driving the bus completely. I definitely have developed and learned things I never thought I would have to learn about. Or have interest in.”</p>
Connecting with sources of pleasure	<p>“Life is still I’m still here, he’s still, you know you’re still alive. Like I say, it’s a beautiful day. I started out with it’s a beautiful day. Right, you know so I’m thankful for the fact that it’s, in San Francisco, it’s almost eighty degrees, which is unheard of, you know. I’m out there in shorts.”</p> <p>“I have 2 dogs, yea. Two little Chihuahua - well, 2 little - one’s a Chihuahua, one’s just the devil I think. They’re not big, but their small. But yeah, I love my animals and my plants and my animals are what keep me going.”</p>

Table 5: Qualitative interview themes and representative caregiver quotations (N=19).

acknowledged that despite caring for a patient suffering from a rare disease, they still felt agency in their choices to maximize their own quality of life or to maintain attitudes characterized by recognition of the potential positive aspects of their experience. Caregivers also described strengthening interpersonal connections and

the desire to help others, including future cancer patients and other caregivers. Many participants also reported strengthening their connection with the patient through their caregiving experience. Moreover, caregivers expressed being motivated by the illness and caregiving experience, finding internal strength through

becoming a highly competent and informed caregiver. Connecting with sources of pleasure was a positive coping strategy for many participants.

Discussion

This mixed-methods study is the first to comprehensively describe the experiences of caregivers of patients with ECD and other HN. High levels of caregiver unmet needs, which were most prevalent in the domains of information and emotional/psychological support, were consistent with other studies of cancer caregivers that document information as the greatest unmet need.³² In the context of rare diseases, unmet informational needs are likely magnified given the paucity of information readily available. Indeed, our qualitative findings underscore a lack of information as a salient concern among ECD/HN caregivers. When left unmet, informational needs have the potential to contribute to psychological and physical health consequences over time³³ and thus crucial to recognize and address.

The capacity of ECD and HN caregivers to derive positive value from caregiving (benefit finding) and connect with a sense of meaning and purpose (meaning-making), despite unmet needs, supports the burgeoning literature documenting caregiver resilience and growth,^{14,34} and importantly, extends it to rare cancer caregivers. Our qualitative results suggest that even though caregivers experienced suffering, they noticed increased social connectedness, appreciation for life, and motivation for productivity. These promising findings highlight the capacity for benefit finding and meaning-making despite the isolating and uncertain nature of ECD and HN. In previous studies, benefit finding was more likely to occur when the cancer was moderately life-threatening with a somewhat uncertain prognosis compared to both curable and incurable cancer diagnoses.³⁵ This may explain why so many ECD/HN caregivers reported positive experiences as they face a rare yet increasingly treatable disease.

We identified certain factors associated with the extent to which rare cancer caregivers undergo positive changes, which can inform targeted interventions aimed to foster benefit finding and meaning-making. Caregivers with unmet informational, psychological/emotional, and social support needs, difficulty tolerating uncertainty, a longer duration of total illness, lower social support and more family conflict, and elevated anxiety and depression symptoms demonstrated less benefit finding and meaning-making. Our findings are reflective of the extant literature in cancer caregivers,^{14,34,36} but extend them to this unique population of rare cancer caregivers in which information is scarce and a period of undiagnosed illness of often extended. Our qualitative interview data also reflected the lasting experiential consequences of grappling with HN illness without adequate information and understanding.

The challenges and unfavorable experiences identified in our study undoubtedly emerge, in part, from providing support for a patient with cancer generally, not exclusively from the rarity of HN. Hematological malignancies often require significant health literacy in the patient and caregiver. They also have a vast range of presentations, which can be challenging in terms of caregivers knowing what to expect or how to interpret the information accessed. A recent review compiled prior studies of caregivers of patients with mixed hematological malignancies ($n = 423$) and demonstrated psychological needs in 38% and relationship/social needs in 20% of caregivers.³⁷ Our data would suggest a markedly higher frequency of unmet needs amongst this rare cancer caregiver population. Therefore, while caregiver distress is multiply determined and derived varied challenges inherit in HN caregiving, the experience of coping with a rare cancer is likely a contributor to additional and unique needs for supportive care which warrant future longitudinal investigation.

Moreover, higher levels of social support, access to information and lower uncertainty have been associated with caregiver resilience in studies of caregivers of patients with more common cancers like breast, prostate and colorectal.¹⁴ Caregivers in those disease groups typically have access to many informational resources and networks of others who have gone through the same experiences. ECD and HN, and the unique challenges associated with taking care of a patient with a rare cancer, may lead to amplified unmet informational and support needs and intolerance of uncertainty that hinder benefit finding and meaning-making.

Many of these factors associated with positive elements of caregiving are readily amenable to rational and feasible psychosocial interventions. Informational and psychological support needs can be addressed in tandem. ECD and HN patients, and those with rare cancers generally, can be directed to advocacy organizations that present synthesized, updated, and lay-friendly education materials. Providers for ECD and HN patients should make all efforts to proactively inquire about whether patients and caregivers have unanswered questions about the disease process, its management or what the future holds. Published guidelines for ECD³⁸ and other HN^{39,40} can be reviewed by healthcare providers to glean up-to-date and evidence-based evaluation and management strategies. We would advocate that providers unfamiliar with ECD and HN have a low threshold to refer patients and caregivers to tertiary centers or formally recognized referral centers⁴¹ with extensive familiarity with these diseases. Optimizing access to informational support may help caregivers derive the greatest possible positive elements of their experience.

While formal efforts for oncology providers to effectively communicate and provide education are essential clinical interventions, ECD and HN caregivers may require additional psychosocial support to help them

manage uncertainty associated with a rare disease, facilitate acceptance, and reduce anxiety and depression symptoms. Evidence-based treatments including both Cognitive Behavioral Therapy and Acceptance and Commitment Therapy^{42,43} have robust evidence for reducing intolerance of uncertainty. Group and/or family focused interventions may facilitate support and improve family communication and have demonstrated efficacy in caregivers.⁴⁴ There is also growing support for evidence-based treatments designed to enhance caregivers' sense of meaning and purpose despite the challenges of caregiving (i.e., Meaning-Centered Psychotherapy for Cancer Caregivers [MCP-C]),⁴⁵ which may directly facilitate benefit finding and meaning-making among caregivers of patients with rare diseases. Clinicians and researchers should aim to optimize these interventions for caregivers as both benefit finding and meaning-making can mitigate the possible negative health consequences associated with coping with a chronic illness.^{46–49} Dedicated support for HN caregivers is also available through the ECD Global Alliance (erdheim-chester.org) and Histiocytosis Association (histio.org).

Limitations of the current study and opportunities for future research should be noted. Analyses were cross-sectional, and as such, our results do not imply directionality and inferences regarding unmet needs as antecedents to caregiver outcomes are limited. Our findings underscore the importance for future investigations to longitudinally assess the associations between caregiver unmet need and psychosocial sequelae. Nonetheless, our qualitative findings complement the quantitative data as caregivers reported their perceptions of the roles of various experiences and stressors in their current functioning. Moreover, while our sample size may seem modest, for a disease as rare as ECD and HN, it is the largest and only analyzed caregiver cohort to date. Our sample was largely comprised of white and highly educated women, which limits generalizability of findings. While men are more likely than women to have ECD, future longitudinal studies with larger, more diverse samples are needed to capture the experience of these caregivers more comprehensively over time.

Our sample also only included caregivers willing to participate in this mixed methods study and within the United States, which could pose selection bias. Our inclusion of caregivers of patients in the U.S. limits generalizability to other contexts and reflects the challenges specific to the U.S. healthcare system, which increasingly relies on the family without providing adequate support such as paid leave, likely amplifying unmet needs. The study also relied on caregiver self-report, which is inherent to psychosocial and quality of life research, but as such, the sample may represent caregivers particularly willing to participate. It is also possible that our sample includes caregivers with more time and resources to facilitate their participation in the study. Therefore, our results may underestimate the

unmet needs of the broader population of ECD/HN caregivers.

This mixed-methods study serves an important role in characterizing the experiences, unmet needs, and opportunities for finding benefit and making meaning among ECD and HN caregivers. As rare cancers, in aggregate, account for approximately 20% of all cancer diagnoses in the United States,⁵⁰ the collective burden of rare cancer caregiving is substantial. The current findings also provide broader insight and opportunities to improve research and clinical care for caregivers of patients with rare cancers more generally. Together, the quantitative and qualitative results reveal salient caregiver concerns that appear related to the rarity of ECD and HN such as lack of information and social support and uncertainty. Despite these challenges, the rare cancer caregivers demonstrated capacity for growth. The factors associated with benefit finding and meaning-making should be examined in future longitudinal investigation as potential targets for supportive interventions that provide information and address psychosocial concerns, with the goal to reduce the potential long-term sequelae associated with rare cancer caregiving.

Contributors

Hannah-Rose Mitchell: Writing-original draft, writing-review & editing, conceptualization, formal analysis, visualization, validation, interpretation; Allison J. Applebaum: Writing- review & editing, conceptualization, supervision, methodology, formal analysis, validation, interpretation; Kathleen A. Lynch: Writing- review & editing, methodology, formal analysis, validation, interpretation; Anne S. Reiner: Writing- review & editing, conceptualization, data curation, formal analysis, methodology; Justin B. Buthorn: Investigation, data collection, writing-review and editing; Allison S. Sigler: Investigation, data collection, writing-review and editing; Dana Bossert: Investigation, data collection, writing-review and editing; Kathleen Brewer: Conceptualization, writing-review and editing; Jessica Corkran: Conceptualization, writing-review and editing; Deanna Fornier: Conceptualization, writing-review and editing; Katherine S. Panageas: Conceptualization, interpretation, writing-review and editing; Eli L. Diamond: Writing-original draft, writing-review & editing

Data sharing statement

The dataset used for this study are available from the corresponding author upon reasonable request.

Declaration of interests

Dr. Applebaum receives support from Blue Note Therapeutics. Dr. Diamond discloses unpaid editorial

support from Pfizer Inc and serves on an advisory board for Day One Therapeutics and Springworks Therapeutics, both outside the submitted work and serves on the Histiocytosis Association Board of Trustees (unpaid) and Erdheim-Chester Disease Global Alliance -Medical Advisory Board (unpaid).

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