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Erdheim–Chester disease: A systematic review

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Contents

Abstract

Erdheim–Chester disease (ECD) is a rare form of non-Langerhans-cell histiocytosis, associated in more than 50% of cases to *BRAF*^{V600E} mutations in early multipotent myelomonocytic precursors or in tissue-resident histiocytes. It encompasses a spectrum of disorders ranging from asymptomatic bone lesions to multisystemic, life-threatening variants. We reviewed all published reports of histologically-confirmed ECD and explored clinical, radiological, prognostic and therapeutic characteristics in a population of 448 patients, including a unique patient from our Department. To find a clinically relevant signature defining differentiated prognostic profiles, the patients' disease features were compared in relation to their CNS involvement that occurred in 56% of the entire population. Diabetes insipidus, visual disturbances, pyramidal and extra-pyramidal syndromes were the most recurrent neurological signs, whereas concomitant pituitary involvement, retro-orbital masses and axial lesions in the presence of symmetric bilateral osteosclerosis of long bones depicted the typical ECD clinical picture. Patients

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with CNS infiltration showed a lower occurrence of heart involvement and a higher incidence of bone, skin, retro-peritoneal, lung, aortic and renal infiltration. No difference in the therapeutic algorithm was found after stratification for CNS involvement. A better understanding of the disease pathogenesis, including *BRAF* deregulation, in keeping with improved prognostic criteria, will provide novel suggestions for the management of ECD.

Keywords: Erdheim–Chester disease; CNS involvement; Histiocytosis; $BRAF^{V600E}$; Vemurafenib

1. Introduction

Erdheim–Chester disease (ECD) is a non-Langerhans-cell form of histiocytosis characterized by xanthomatous infiltration of tissues by CD68-positive, CD1a-/S100-negative foamy histiocytes [1]. It is a rare disorder accounting for up to 600 cases to date, which primarily affects male patients between their 5th and 7th decade of life [2]. Although, according to the WHO classification, ECD is a neoplasm deriving from histiocytes, there is a long standing debate as to whether the disorder is of malignant or polyclonal reactive nature [3]. Clinical manifestations of ECD at presentation are protean and encompass bone pain, diabetes insipidus, neurological and constitutional symptoms, although retroperitoneal, cutaneous, cardiovascular and pulmonary involvement have also been described [4,5]. Since the clinical picture of ECD arises as a slowly forming mosaic with sequential manifestations, the diagnosis is often challenging. However, X-ray peculiar aspects such as symmetric diaphyseal osteosclerosis or parallel scintigraphy uptake in long bones of both extremities provide a striking signature of the disease and may favor the diagnosis [2].

Recently, the discovery of activating mutations of *BRAF* in 54% of ECD patients, along with the role of tumor microenvironment in its development, has modified the traditional interpretation of the disease, supporting novel therapeutic potential in adopting the targeted therapy [6–8]. In particular, the *BRAF* inhibitor Vemurafenib [9], the anti-TNFα moAb Infliximab [10], and the IL-1R antagonist Anakinra [11] have been used with variable though promising results. However, the 5-year survival occurs in less than 70% of patients [12].

Based on the availability of new drugs, some of which exceeding the blood–brain barrier, optimized treatments for patients with CNS lesions are urgently needed. Here, we report a single case of ECD and systematically revisit all published, reliably diagnosed cases of ECD.

2. Case report

A 28-year-old man with a 5-year history of diabetes insipidus, vespertine fever, dyspepsia, nausea and vomiting was admitted in 2010 at our Department complaining of paresthesia and weakness of the lower extremities. Physical examination demonstrated mild left hand dysmetria, ataxic gait as well as the presence of bilateral eyelid xanthelasmas and well-defined papules on the thoracic wall. The results of extensive serum laboratory analyses were otherwise unremarkable. The brain MRI documented a homogeneous intense enhancement of infundibular stalk (Fig. 1A) after gadolinium administration and the presence of white matter lesions in the pons and in the right middle cerebellar peduncle (Fig. 1B). Spinal cord involvement was also detected, since several lesions with moderate contrast enhancement on T1 sequence were diagnosed at level of C2, D1, D8 and D10–D11 (Fig. 1G). The ^{99}Tec-bone scan showed increased uptake in the proximal epiphysis and metaphysis of long bones (Fig. 1D), while 18FDG-PET/CT demonstrated high glucose avidity of the brain lesions with a SUV up to 7.3 in the pituitary gland (Fig. 1C). The patient was subjected to rachicentesis, but the cerebrospinal fluid analysis was unremarkable, showing only rare lymphocytes and histiocytes. Treatment with desmopressin and prednisone was started, but neurological symptoms exacerbated. A skin lesion biopsy revealed the presence of small nucleated foamy histiocytes (CD1a−, CD68+, S100−) and Touton-like multinucleated giant cells along with lymphocytic and eosinophilic infiltration (Fig. 1I–J). These findings suggested the diagnosis of ECD, and therapy with cyclophosphamide was initiated. After one year of treatment, ataxia, paresthesias and weakness of lower extremities worsened with raising of dizziness, diplopia and blurred vision. A new brain MRI showed additional areas of increased contrast-uptake in the right cerebellar hemisphere (Fig. 1E), in the left parietal lobe in close proximity to the ipsilateral lateral ventricle and in the splenium of the corpus callosum (Fig. 1F) in concomitance with worsening of the multiple spinal lesions, while a new sclerotic area involving the L2 vertebra was detected (Fig. 1H). Cyclophosphamide was discontinued and the patient started the treatment with alfa-2b Peg-interferon at 120 μg/week. Since this single-drug therapy did not improve the neurological symptoms, the interferon dosage was increased to 180 μg/week, in conjunction with low dosage of prednisone and cyclophosphamide. At the last follow-up, in June 2013, a partial regression of the brain lesions was detected by both MRI and 18FDG-PET/CT, and the treatment was maintained. Based on the study by Haroche et al. [6], analysis of *BRAF* mutational status was performed by pyrosequencing, and the V600E mutation was detected.

3. Literature review and methods of analysis

We searched the English-language literature indexed in PubMed using the keyword “Erdheim–Chester disease” and

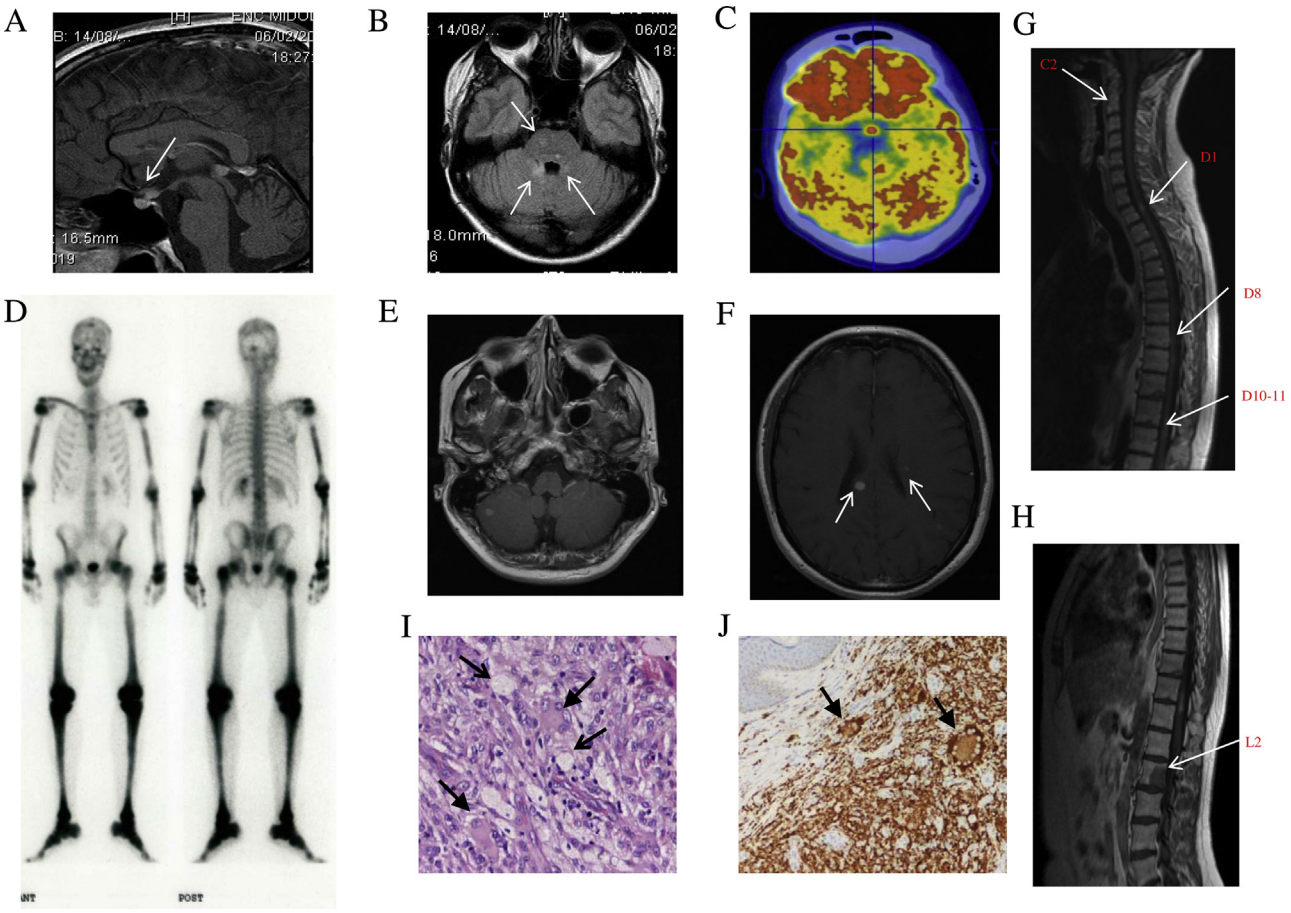

Fig. 1. *Bone and CNS involvement in our own observation of ECD.* At diagnosis, MRI detected an intense enhancement of the infundibular stalk after gadolinium administration (A) and the presence of white matter lesions in the pons and in the right middle cerebellar peduncle (B). Fused PET/CT image (C) showed increased FDG uptake in the pituitary gland. ^{99}Tec bone scan showed increased uptake in the proximal epiphysis and metaphysis of long bones (D). After one year of treatment with cyclophosphamide and steroids, the patient underwent worsening in the CNS involvement, with new cerebellar (E) and peri-ventricular lesions (F). Also, spinal (G) and vertebral (H) lesions were detected. CD68+ small nucleated foamy histiocytes (arrow) and Touton-like multinucleated giant cells (arrowhead) in a skin lesion biopsy (I–J).

published up to June 2014. Among the described cases, diagnosis of ECD was considered consistent when the criteria proposed by Haroche et al. (Table 1) [2] were fulfilled. Only papers reporting data from individual patients were included for review. Cases with doubtful or not univocal diagnosis as well as repeated reports on the same patients were excluded.

Table 1
Diagnostic criteria for ECD proposed by Haroche et al.

1. Characteristic histological findings	Foamy histiocyte infiltration of polymorphic granuloma and fibrosis or xanthogranulomatosis, with CD68-positive and CD1a negative immunostaining
2. Characteristic skeletal abnormalities*	(a) Bilateral and symmetric cortical osteosclerosis of the diaphyseal and metaphyseal parts of the long bones on X-rays, and/or (b) Symmetric and abnormally intense labeling of the distal ends of the long bones of the legs, and in some cases arms, as revealed by ^{99}Tc bone scintigraphy.

* The second criterion is not strictly required for ECD diagnosis.

In particular, three independent physicians (V.S., F.M.R. and M.C.L.) reviewed the selected papers and completed a detailed analysis of clinical, pathological and radiological features as well as treatment and outcome. Details included age at the onset of ECD, sex, race, main neurological signs and symptoms, results of the morphological and functional imaging, molecular assessment, treatments and follow-up. In this reviewing analysis we obviously included our own clinical observation.

Statistical analysis was performed using GraphPad Prism 5 software for Macintosh (GraphPad Software, La Jolla, CA, USA). Differences between groups of patients were tested using Student's t test and the Mann–Whitney test for continuous data, while the Fischer exact test, the χ^2 test or the Mann–Whitney test were used for categorical data. Overall survival (OS) was determined from diagnosis to death from any cause. Survival curves were estimated using the method of Kaplan–Meier and were compared by the log-rank test. All tests were two-sided, and a p-value <0.05 was considered statistically significant.

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4. Results

4.1. Patient population

From the systematic review of the literature, we retrieved 331 manuscripts describing patients with ECD (Table S1). In 448 patients the ECD diagnosis was considered consistent. Median age at diagnosis in the population of patients with neurological involvement was 51.5 years (range, 4–77) and was lower with highly significant difference ($p = 0.002$) compared to patients without neurological symptoms (54.5 years). Comparison by sex using the Dunn's post-test failed to show any significant difference in the median age at diagnosis between the two cohorts of patients ($p > 0.05$, data not shown). In the overall population the median age at death, and mean time between diagnosis and death were 56 and 2.3 years, respectively (Table 2).

4.2. Neurological manifestations

Neurological symptoms represent a prominent feature of ECD and occur in approximately 25% and 50% of patients at the onset or during the course of the disease, respectively. Exophthalmos, gaze disturbances, diabetes insipidus, cerebellar syndromes, seizure and focal mass lesions-related radiculopathy are the most recurrent manifestations affecting the central nervous system (CNS), whose lesions are directly responsible for one third of all deaths and have been specifically identified as independent predictive factors of poor prognosis [4,12]. In our case record, only 11 patients displayed no neurological symptoms despite their radiologic findings were consistent with CNS involvement. As represented in Fig. 2A, diabetes insipidus was the most common manifestation of neuro-ECD and was associated with thickening of the pituitary stalk, alteration of the brightness of the hypophysis or pituitary infiltration in 12%, 6% and 3% of patients, respectively. Unspecific neuroradiologic patterns were found in the other patients. Up to 72% of those with diabetes insipidus showed other sites of the disease within the CNS as visual disturbances, diplopia and blurred vision, whereas ataxia was revealed in approximately 23% of patients and was associated to lesions involving the retrobulbar fat or the optic chiasm, and the cerebellum lobes or the dentate area. Patients with ataxia frequently displayed dysmetria, nystagmus, positivity of the Babinski sign and/or tendon hyperreflexia at the physical examination (Fig. 2B). Perturbations of the pyramidal system were also described as hemiparesis or paraparesis that were reported in 7% of patients, usually as consequence of spine compression by intradural masses or, most often, extradural and bony lesions. Dysarthria, headache, epilepsy and neuropsychiatric symptoms including delirium, psychosis, depression and cognitive function deterioration were observed in less than 10% of patients with neurological involvement and were commonly associated to lesions involving the cerebral lobes.

Symptoms consistent with hypopituitarism were documented in 6% of the study population, whereas intracranial hypertension syndrome with nausea, vomiting and papilledema was reported in a minority (2.5%) of patients, irrespective of the number, location and size of their axial lesions. Among the signs of CNS involvement (Fig. 2B), exophthalmos was the most common, being reported in 37% of patients. Exophthalmos presented both unilaterally or bilaterally and was the clinical appearance of a retro-orbital mass in 98% of cases.

Neuropathological imaging is essential for both diagnosis and prognosis, and includes retro-orbital masses, involvement of cerebellum dentate nucleus, meningeal lesions of the dura, and multiple areas of demyelination of both cerebellum and brainstem. Suprasellar lesions and/or nodular or micronodular masses of the infundibular stalk are associated with diabetes insipidus, hypopituitarism and hyperprolactinemia as consequence of the disruption of the hypothalamic dopaminergic prolactin inhibiting pathway [3,13]. As shown in Fig. 2C, the described SNC lesions were ubiquitous, involving the brain, the brainstem and, less frequently, the spine. No pathognomonic neuroradiological pattern of CNS involvement could be recognized. Up to 17% of patients showed unspecific patterns such as widespread hyperintense signals on T2-weighted MRI images, or white matter lesions, whereas meningeal lesions were found in up to 10% of neuro-ECD patients. Over 50% of patients had simultaneous involvement of at least two anatomical sites within the CNS.

Extra-neurological manifestations are summarized in Table 3.

4.3. Bone involvement

Skeletal localizations were described in 74% of patients during the entire course of the disease. The most affected bones were femur and tibia, and symmetric diaphyseal osteosclerosis or symmetric uptake of long bone extremities at bone scan were the most common imaging findings. Frequency of skeletal involvement was not influenced by the sex, and the mean age at diagnosis in the presence of bone lesions was 51 years. Although an increased incidence (86%) of skeletal involvement was found in younger patients (age ≤ 25), no significant difference was observed after stratification for age groups ($p = 0.357$).

4.4. Retroperitoneal and renal infiltration

Retroperitoneal involvement was described in more than one third of patients with ECD and was often asymptomatic. Of note, the frequency of pseudo "retroperitoneal fibrosis" was significantly increased in male patients ($p < 0.0001$), whereas no difference was seen in terms of age distribution. Kidney infiltration or renal obstructive impairment with consequent hydronephrosis was described in 6% of the overall population and was often associated with the presence of retroperitoneal lesions and the X-ray appearance of "hairy

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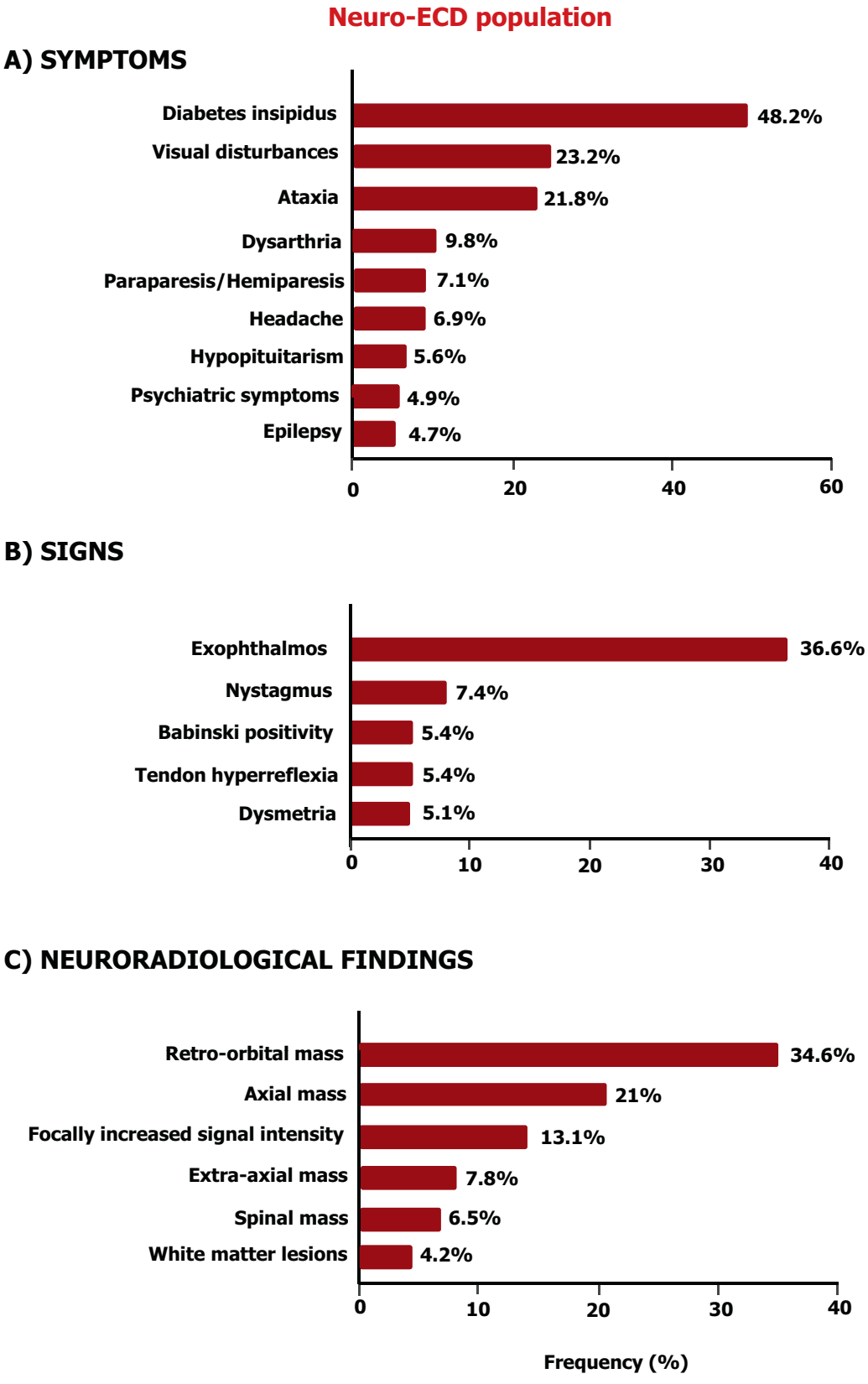

Fig. 2. *Spectrum of clinical features in patients with neurological involvement.*

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Table 2
Patient demographics according to the CNS involvement status.

Characteristics	Cumulative population	With neurological involvement 249 (55.6%)	Without neurological involvement 199 (44.4%)	*p*-Value
				Neuro-ECD vs non neuro-ECD*
Sex				0.12
Male, *n* (%)	277 (61.8%)	163 (65.5%)	114 (57.3%)	
Female, *n* (%)	169 (37.7%)	86 (34.5%)	83 (41.7%)	
Not reported, *n* (%)	2 (0.5%)		2 (1%)	
Race				0.15
White, *n* (%)	50 (11.6%)	25 (10.5%)	25 (13%)	
Black, *n* (%)	7 (1.6%)	2 (0.8%)	5 (2.6%)	
Asian, *n* (%)	22 (5.1%)	9 (3.7%)	13 (6.8%)	
Not reported, *n* (%)	369 (81.6%)	213 (85%)	156 (77.6%)	
Age at diagnosis (years)				0.002
Mean (±SD)	51 (±15.1)	49 (±14.1)	53.4 (±15.9)	
Median	53	51.5	54.5	
Range	4–87	4–77	10–87	
Age at death (years)				0.82
Mean (±SD)	55.4 (±12)	55 (±11.8)	56.3 (±13.1)	
Median	56	55	58.5	
Range	26–77	26–74	35–77	
Overall survival (years)				0.24
Mean (±SD)	2.3 (±3.4)	2.6 (±3.8)	1.5 (±2.1)	
Median	1	1	1	
Range	0–17	0–17	0–7	

* *p*-Values computed using Mann–Whitney test, Fisher exact test or χ^2 test, as appropriate.

kidneys". This finding, due to the perirenal fat infiltration, appears as an irregular renal border that is emphasized by iodinated contrast and is useful for differential diagnosis with idiopathic or secondary retroperitoneal fibrosis.

4.5. Lung and cardiovascular involvement

Infiltration of the lung parenchyma was reported in 18% of patients who presented cough and dyspnea, whereas 36% were diagnosed with cardiovascular involvement. In particular, the most frequent cardiovascular site of disease was the thoracic and abdominal aorta, with a pattern of circumferential peri-adventitial infiltration ("coated aorta" appearance) that may extend to main aortic branches. Heart and coronary "pseudo-tumoral" infiltration as well as pleural and pericardial involvement were reported in 11% and 9% of the cumulative patient population, respectively. Mean age at diagnosis of ECD in the presence of heart involvement was 60 years, whereas no heart and/or pleuro-pericardial involvement was described in younger patients. Notably, the occurrence of heart involvement was significantly higher in older patients ($p = 0.028$).

4.6. Skin involvement

Cutaneous manifestations affected 27% of patients with ECD. Xanthelasmas were the most commonly reported skin lesions, while xanthoma-like papules and mucosal infiltration of the genital area accounted for less than 1% of dermatologic manifestations. Skin involvement was described mostly in older patients ($p = 0.007$).

4.7. Systemic manifestations with respect to CNS involvement

To determine if the occurrence of the CNS involvement is associated with a specific pattern of extra-neurological manifestations, we compared the anatomic distribution of ECD lesions in patients with and without neurological symptoms. As depicted in Fig. 3, patients harboring lesions of the CNS displayed an increased though not significant incidence of bone, cutaneous, retroperitoneal, lung and aortic involvement. In particular, the occurrence of kidney involvement (kidney infiltration and/or "hairy kidney" aspect and/or hydronephrosis) was higher in the neuro-ECD population ($p = 0.001$), probably reflecting a more systemic involvement in this group of patients. A non-significant inverse correlation was found between heart and CNS disease localization.

4.8. Treatment

More than 72% of treated patients with ECD received corticosteroids (Table 4), both by oral or intravenous administration. Interferon was used in almost 32% of patients, with doses widely ranging from 3 to 9 MU × 3 per week and 120 to 200 μg per week in the non-pegylated and pegylated form,

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Table 3
Extra-neurological disease localization detected by imaging diagnostic procedures in a cohort of 448 patients with ECD.

Disease localization	Cumulative population	Sex distribution			Age at diagnosis		Age distribution		
		Males ($n=277$)	Females ($n=169$)	p-Value*	Mean (±SD) (years)	Age ≤25 ($n=28$)	Age 26–60 ($n=300$)	Age >60 ($n=119$)	p-Value*
Bone, n (%)	332 (74.1%)	208 (75.1%)	124 (73.4%)	0.69	50.8 (±15.3)	24 (85.7%)	221 (73.7%)	87 (73.1%)	0.357
Retroperitoneum, n (%)	162 (36.2%)	122 (44%)	40 (23.7%)	<0.0001	52.8 (±12.5)	5 (17.8%)	115 (38.3%)	42 (35.3%)	0.095
Lung, n (%)	82 (18.5%)	55 (19.9%)	27 (16%)	0.3	51.7 (±16)	6 (21.4%)	48 (16%)	28 (23.5%)	0.181
Great vessels, n (%)	73 (16.3%)	51 (18.4%)	22 (13%)	0.135	54.8 (±12.2)	1 (3.6%)	48 (16%)	24 (20.2%)	0.098
Heart, n (%)	48 (10.7%)	28 (10.1%)	20 (11.8%)	0.568	60.1 (±9.5)	0	29 (9.7%)	19 (16%)	0.028
Pleuro-pericardial membrane#, n (%)	40 (8.9%)	30 (10.8%)	10 (5.9%)	0.078	52.6 (±14.4)	0	27 (9%)	13 (10.9%)	0.19
Kidney, n (%)	27 (6%)	20 (7.2%)	7 (4.1%)	0.186	49 (±15.5)	2 (7.1%)	20 (6.7%)	5 (4.2%)	0.613
Skin, n (%)	120 (26.8%)	62 (22.4%)	58 (34.3%)	0.737	52.2 (±12.1)	1 (3.6%)	80 (26.7%)	39 (32.8%)	0.007

* p-Values computed using χ^2 test or Student's t test, as appropriate.
# Pleural and/or pericardial effusion and/or infiltration without apparent involvement of the heart.

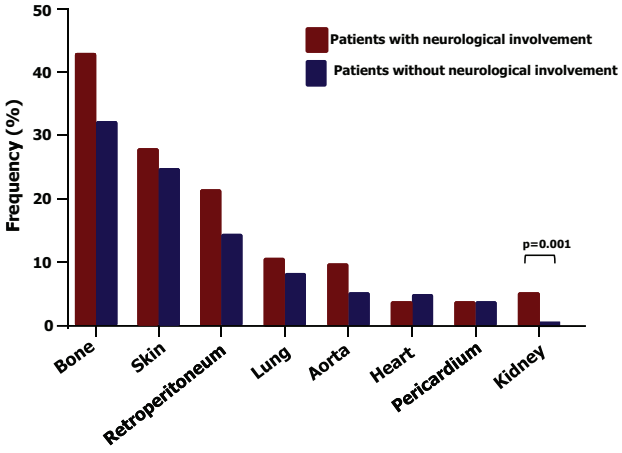

Fig. 3. *Frequency of disease localizations in patients with ECD.*

respectively. Drug tolerance was often reported as poor. Up to 13% and 6% of patients were subjected to radiotherapy or surgery on brain and bone lesions. A number of chemotherapeutic agents were also used during the course of the disease, including vinblastine (12%), cladribin (5%), vincristine (4%) and etoposide (3%). The use of high-dose chemotherapy regimens was reported for the minority of patients undergoing adult stem cell transplantation (1%). Immunosuppressive agents included cyclophosphamide (12%), methotrexate (6%), azathioprine (4%) and cyclosporine (2%) (Table 4).

In recent years, targeted agents have been increasingly used, namely Imatinib, Infliximab and the recombinant human interleukin-1 receptor Anakinra. Based on the reported dramatic efficacy, it is conceivable that the use of Vemurafenib, up to date administered in only five patients [9,14,15], will increase in next years (Fig. 4). Up to 4% of patients were subjected to antiresorptive therapy with bisphosphonates. Efficacy of these treatments remains undefined

Table 4
Chronologic introduction of different drugs used as single or combinatory agents to treat ECD.

Year of introduction	Drug
1982	Corticosteroids (CS)
1990	Vinblastine (CHT)
1990	Cyclophosphamide (CHT)
1990	Methotrexate (CHT)
1993	Azathioprine (IS)
1997	Interferon (BD)
1997	Cyclosporine (IS)
1999	Etoposide (CHT)
2000	Cladribine (CHT)
2000	Vincristine (CHT)
2008	Imatinib (TKI)
2010	Anakinra (BD)
2012	Infliximab (BD)
2013	Vemurafenib (TKI)

Legend of acronyms for class of drugs: CS: corticosteroids; CHT: chemotherapeutic agent; IS: immunosuppressant; BD: biological drug; TKI: tyrosine kinase inhibitor.

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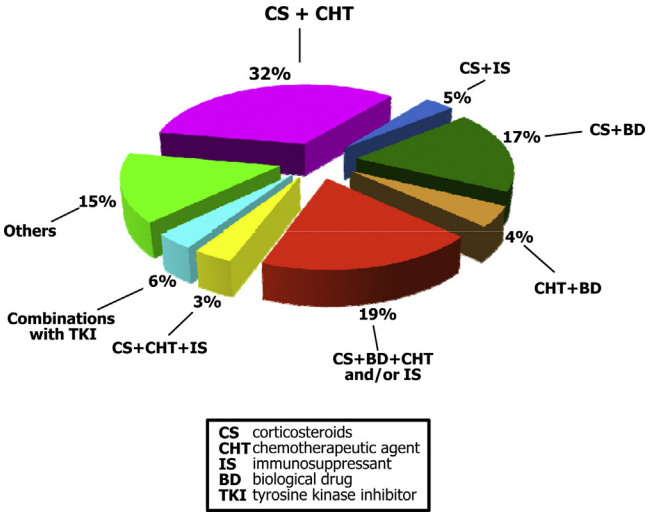

Fig. 4. *Treatment of ECD.* Percentages of the combination medical therapies used for ECD treatment.

due to the frequent concomitant administration of more than one drug and to the short follow-up.

Finally, data concerning the OS were reported only in 39 patients with CNS involvement and in 18 without CNS involvement, thus making impossible to draw any reliable conclusion. Nevertheless, comparison of survival curves revealed no significant difference in the prognosis of patients with and without neurological symptoms ($p = 0.24$).

5. Discussion

During the last decades histiocytoses have been described as a collection of highly heterogeneous clinical manifestations connected only by a common histopathology. Despite its rarity, ECD includes clinically variable disorders that range from asymptomatic bone infiltration to multiorganic diseases and its clinical course is determined by the extent and distribution of the disease [2]. Recently, major genetic and molecular advances including the detection of recurrent *BRAF*^{V600E} gain-of-function mutations in biopsies and in peripheral blood of ECD patients [6,16], as well as the recognition of *BRAF* aberrations in early myelomonocytic precursors or in hematopoietic stem cells of patients with Langerhans cell histiocytosis (LCH) [17], have supported the hypothesis that histiocytoses are myeloid neoplasms.

CNS involvement has been traditionally considered an adverse prognostic feature in various forms of myeloid malignancies, requiring the use of both preventive and CNS-directed therapy [18–22]. Similarly, a poorer prognosis has been claimed for ECD patients harboring CNS lesions as compared to those without CNS involvement [12], but no definite evidence is currently available. However, some controversy regarding the proper definition of CNS involvement itself has been raised in recent years, with diabetes insipidus and exophthalmos being alternatively included or not as CNS manifestation by different Authors [3–5,23,28].

We identified 448 patients with a reliable diagnosis of ECD. According to previous findings [4,12], CNS involvement (including diabetes insipidus and exophthalmos) was reported in 56% of the overall population and was the second most common site of disease after bone. Of note, the presence of neurological symptoms led to a significant anticipation of the diagnosis, consistent with a more aggressive course of the disease, a more accurate diagnostic work-up, or both. This was particularly evident in our patient, in whom neurologic symptoms dominated both the clinical presentation and the course of the disease. Although young age, male sex, diabetes insipidus, ataxia, weakness of lower extremities and diplopia are common findings in ECD, the rarity of the disease hindered the diagnosis and necessitated an extensive diagnostic pathway, in which bone scan and MRI of the CNS were essential components. Based on our observation (Fig. 2C) and in spite of the reported rarity of spinal cord involvement [23], we propose that the spine should be routinely evaluated by MRI when ECD is suspected.

Diabetes insipidus was one of the most common manifestations both at presentation [4] and during the course of the disease. It was typically associated with thickening of the pituitary stalk, alteration of the brightness of the hypophysis or a neuroradiologic pattern of pituitary infiltration. A minority of patients with diabetes insipidus displayed also signs of hypopituitarism. Replacement of the posterior pituitary by xanthogranulomatous infiltrates is a common finding in ECD and can lead to a decrease in the function of the anterior pituitary consequent to the destruction of the hypophyseal stalk and the compression on the hypothalamus [24].

Infections including tuberculous pachymeningitis, Whipple's disease, pituitary abscess, coccidioidomycosis and aspergillosis; vasculitis such as Wegener's granulomatosis, Takayasu's arteritis, neurosarcoidosis, Cogan's syndrome and lymphocytic hypophysitis; or expansive/infiltrative processes such as Langerhans cell histiocytosis, germinoma, amyloidosis and hemochromatosis can present with diabetes insipidus in the presence of a sellar mass and should therefore be considered in the differential diagnosis [25,26]. Since diabetes insipidus is an early manifestation [4], a high level of diagnostic suspicion and a thorough neurological evaluation is required. We found a clear-cut correlation between diabetes insipidus and extra-pituitary CNS involvement. Moreover, based on its high specificity for brain ECD lesions [27], PET scanning should be considered for the initial assessment and follow-up of ECD patients displaying pituitary involvement (Fig. 1C). Visual disturbances and unilateral or bilateral exophthalmos were found in 20% of the cumulative patient population and were mostly related to retro-orbital masses or lesions compressing the optic nerve or the optic chiasm. Cerebral and cerebellar lesions caused pyramidal and extrapyramidal syndromes, respectively, but signs of intracranial hypertension were rarely reported, suggesting that CNS lesions in ECD patients are slowly progressive.

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We confirmed the distinction in the infiltrative, meningeal and composite patterns of neuroradiological involvement proposed in 2006 [13]. However, although we recognized axial lesions and widespread cerebral hyperintensity as the most common neuroradiological findings, the overall meningeal involvement was underrepresented as compared with previous reports [13,28]. Since a multifocal involvement of CNS and orbits was a frequent event, we propose that pituitary involvement, retro-orbital masses and infiltrative axial lesions be considered a neuroradiologic triad strongly suggestive of ECD, at least in the presence of a positive bone scan or osteosclerosis of the facial sinus walls [28].

Bone involvement was the most common manifestation, being documented in up to 74% of patients. It was more common in young patients and was often associated with bone pain. Retroperitoneum was involved in 36% of the ECD population, with a frequency significantly higher in males. Similar data have been reported for Ormond's disease [29], suggesting that sex-related factors play a role in the pathogenesis of the retroperitoneal involvement. Cutaneous manifestations, primarily including xanthelasmas and xanthoma-like papules, were documented in 27% of patients, and their frequency significantly increased with age. Cardiovascular infiltration was diagnosed in 36% of patients, but was restricted to patients older than 25. Moreover, age at diagnosis of heart involvement was significantly higher than in the overall ECD patient population, indicating that the cardiovascular involvement is a late complication of ECD [30]. Of note, patients with neurological involvement showed a strikingly increased incidence of renal infiltration. Overall, our findings are in agreement with those reported in large series [2]. Selection bias and lack of extensive diagnostic work-up in a portion of the patient population may account for the low frequency of the "pseudo-tumoral" infiltration of the right atrium as well as the "hairy kidney" aspect (9% and 6% vs 30% and 68% in our analysis and in other studies [2,31], respectively).

Systemic manifestations of ECD were peculiar and their radiological appearance made the diagnosis rather easy. The symmetric bilateral osteosclerosis of the metaphysis and diaphysis of long bones (74%), the sheathing of the whole thoraco-abdominal aorta called "coated aorta" (16%) and the perirenal fascia infiltration taking the appearance of "hairy kidneys" (6%) are highly suggestive features of the disease.

For decades, corticosteroids, cytotoxic agents such as vinca alkaloids and immunosuppressive agents including cyclophosphamide, methotrexate and azathioprine, represented the therapeutic milestone for ECD patients. More recently, IFN-based therapy has emerged as a reliable option for ECD patients. Response to IFN-α is the only major treatment predictor of survival, in particular in patients with CNS involvement [12,32]. A reliable assessment of the efficacy of the above mentioned treatments was hampered by the concomitant administration of different drugs, lack of dosage information (in particular for IFN-α) and the small number of patients.

Inhibition of *BRAF* activation by Vemurafenib is a highly promising treatment, in particular for its ability to overcome the blood brain barrier [9]. In spite of the small size and the short follow-up of the case series described, dramatic responses were recorded after a few weeks of treatment, emphasizing the pivotal role of *BRAF* mutation in this disease. Mutations of *BRAF* result in a conformational change of a serine/threonine-protein kinase that leads to a chronic activation of *RAS-RAF-MEK-ERK* pathway and, therefore, to accelerated proliferation and survival of cells [33]. The oncogenic activity of *BRAF* mutations has been extensively documented in several neoplasms, traditionally including melanoma [34] and hematologic malignancies such as extra-osseous multiple myeloma [35] as well as the oncogene-induced senescence (OIS), a protective physiological process based on the activation of both p16 and p21 against the oncogenic transformation due to a cell cycle derangement [36,37]. In OIS, senescent cells activate a proinflammatory response, known as senescence-associated secretory phenotype (SASP) [38] that appears similar to the ECD inflammatory status, thus supporting the pathogenetic interpretation of ECD as a full-blown chronic inflammatory disease [16]. Intriguingly, the recent discovery of additional *NRAS* mutations in ECD [39–41] strongly suggests that the entire *RAS-RAF-MEK-ERK* pathway plays a pathogenic role in histiocytosis, thus raising interest in dual *BRAF/MEK* inhibition. Innovative non-invasive tools evaluating BRAF mutations in urine and plasma cell-free DNA have provived excellent reliability in the diagnosis and follow-up of patients with histiocytic disorders [42] to predict outcomes and response to targeted treatments.

Improved understanding of the pathogenetic mechanisms underlying ECD will lead to the development of more effective targeted therapies, while an accurate stratification of patients based on their neurologic involvement will help clinicians to maximize benefits of novel molecular targeting for therapy.

Conflict of interest statement

The Authors declare no affiliation with industries or organizations with a financial interest, direct or indirect, that may affect the conduct or reporting of the work submitted.

Contributions

MC contributed to the design of the study, acquisition, analysis and interpretation of data, and drafting of the article. VS, FMR and MCL contributed to the acquisition, analysis and interpretation of data. Franca Dicuonzo and GI contributed to acquisition of data. FS contributed to drafting and critical revision of the article. Franco Dammacco designed the study and critically revised the article. All Authors have approved the final article version.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.critrevonc.2015.02.004.

References

[1] Haroche J, Arnaud L, Amoura Z. Erdheim–Chester disease. Curr Opin Rheumatol 2012;24(1):53–9.
[2] Haroche J, Arnaud L, Cohen-Aubart F, Hervier B, Charlotte F, Emile JF, et al. Erdheim–Chester disease. Curr Rheumatol Rep 2014;16(4):412.
[3] Mazor RD, Manevich-Mazor M, Shoenfeld Y. Erdheim–Chester disease: a comprehensive review of the literature. Orphanet J Rare Dis 2013;8:137.
[4] Cavalli G, Guglielmi B, Berti A, Campochiaro C, Sabbadini MG, Dagna L. The multifaceted clinical presentations and manifestations of Erdheim–Chester disease: comprehensive review of the literature and of 10 new cases. Ann Rheum Dis 2013;72(10):1691–5.
[5] Diamond EL, Dagna L, Hyman DM, Cavalli G, Janku F, Estrada-Veras J, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim–Chester disease. Blood 2014;124(4):483–92.
[6] Haroche J, Charlotte F, Arnaud L, von Deimling A, Hélias-Rodzewicz Z, Hervier B, et al. High prevalence of BRAF V600E mutations in Erdheim–Chester disease but not in other non-Langerhans cell histiocytoses. Blood 2012;120(13):2700–3.
[7] Rizzo FM, Cives M, Simone V, Silvestris F. New insights into the molecular pathogenesis of Langerhans cell histiocytosis. Oncologist 2014;19(2):151–63.
[8] Munoz J, Janku F, Cohen PR, Kurzrock R. Erdheim–Chester Disease: characteristics and management. Mayo Clin Proc 2014;89(7):985–96.
[9] Haroche J, Cohen-Aubart F, Emile JF, Arnaud L, Maksud P, Charlotte F, et al. Dramatic efficacy of Vemurafenib in both multisystemic and refractory Erdheim–Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. Blood 2013;121(9):1495–500.
[10] Dagna L, Corti A, Langheim S, Guglielmi B, De Cobelli F, Doglioni C, et al. Tumor necrosis factor α as a master regulator of inflammation in Erdheim–Chester disease: rationale for treatment of patients with infliximab. J Clin Oncol 2012;30(28):e286–90.
[11] Aouba A, Georgin-Lavialle S, Pagnoux C, Martin Silva N, Renand A, Galateau-Salle F, et al. Rationale and efficacy of interleukin-1 targeting in Erdheim–Chester disease. Blood 2010;116(20):4070–6.
[12] Arnaud L, Hervier B, Néel A, Hamidou MA, Kahn JE, Wechsler B, et al. CNS involvement and treatment with interferon-α are independent prognostic factors in Erdheim–Chester disease: a multicenter survival analysis of 53 patients. Blood 2011;117(10):2778–82.
[13] Lachenal F, Cotton F, Desmurs-Clavel H, Haroche J, Taillia H, Magy N, et al. Neurological manifestations and neuroradiological presentation of Erdheim–Chester disease: report of 6 cases and systemic review of the literature. J Neurol 2006;253(10):1267–77.
[14] Los Arcos-Bertiz I, Santos-Ortega A, Rodriguez Palomares J, Juanos-Iborra M, Bujan-Rivas S, Tornos-Mas P, Martinez-Valle F. A 72-year-old man with dyspnea, circumferential aortic thickening, and weight loss. Arthritis Care Res (Hoboken) 2013;65(12):2056–61.
[15] Rouco I, Arostegui J, Cánovas A, González Del Tánago J, Fernández I, Zarranz JJ. Neurological manifestations in Erdheim–Chester disease: two case reports. Neurologia 2014, http://dx.doi.org/10.1016/j.nrl.2014.01.010 (ahead of print).
[16] Cangi MG, Biavasco R, Cavalli G, Grassini G, Dal-Cin E, Campochiaro C, et al. BRAFV600E-mutation is invariably present and associated to oncogene-induced senescence in Erdheim–Chester disease. Ann Rheum Dis 2014;211(4):669–83.
[17] Berres ML, Lim KP, Peters T, Price J, Takizawa H, Salmon H, et al. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J Exp Med 2014;211(4):669–83.
[18] Dahl GV, Simone JV, Hustu HO, Mason C. Preventive central nervous system irradiation in children with acute nonlymphocytic leukemia. Cancer 1978;42:2187–92.
[19] Stavem P, Evansen SA. CNS involvement in acute myelomonoblastic leukemia. Br J Haematol 1984;58:383–4.
[20] Pinkel D, Woo S. Prevention and treatment of meningeal leukemia in children. Blood 1994;84:355–66.
[21] Creutzig U, Zimmermann M, Bourquin JP, Dworzak MN, Fleischhack G, von Neuhoff Sander A, et al. CNS irradiation in pediatric acute myeloid leukemia: equal results by 12 or 18 Gy in studies AML-BFM98 and 2004. Pediatr Blood Cancer 2011;57(6):986–92.
[22] Mayadev JS, Douglas JG, Storer BE, Appelbaum FR, Storb R. Impact of cranial irradiation added to intrathecal conditioning in hematopoietic cell transplantation in adult acute myeloid leukemia with central nervous system involvement. Int J Radiat Oncol Biol Phys 2011;80(1):193–8.
[23] Sedrak P, Ketonen L, Hou P, Guha-Thakurta N, Williams MD, Kurzrock R, et al. Erdheim–Chester disease of the central nervous system: new manifestations of a rare disease. AJNR Am J Neuroradiol 2011;32(11):2126–31.
[24] Kovacs K, Bilbao JM, Fornasier VL, Horvath E. Pituitary pathology in Erdheim–Chester disease. Endocr Pathol 2004;15(2):159–66.
[25] Carpinteri R, Patelli I, Casanueva FF, Giustina A. Pituitary tumours: inflammatory and granulomatous expansive lesions of the pituitary. Best Pract Res Clin Endocrinol Metab 2009;23(5):639–50.
[26] Jian F, Bian L, Sun S, Yang J, Chen X, Chen Y, et al. Surgical biopsies in patients with central diabetes insipidus and thickened pituitary stalks. Endocrine 2014;47(1):325–35.
[27] Arnaud L, Malek Z, Archambaud F, Kas A, Toledano D, Drier A, et al. 18F-fluorodeoxyglucose-positron emission tomography scanning is more useful in followup than in the initial assessment of patients with Erdheim–Chester disease. Arthritis Rheum 2009;60(10):3128–38.
[28] Drier A, Haroche J, Savatovsky J, Godenèche G, Dormont D, Chiras J, et al. Cerebral, facial and orbital involvement in Erdheim–Chester disease: CT and MRI findings. Radiology 2010;255(2):586–94.
[29] Kermani TA, Crowson CS, Achenbach SJ, Luthra HS. Idiopathic retroperitoneal fibrosis: a retrospective review of clinical presentation, treatment, and outcomes. Mayo Clin Proc 2011;86(4):297–303.
[30] Haroche J, Amoura Z, Dion E, Wechsler B, Costedoat-Chalumeau N, Cacoub P, et al. Cardiovascular involvement, an overlooked feature of Erdheim–Chester disease: report of 6 new cases and a literature review. Medicine (Baltimore) 2004;83(6):371–92.
[31] Haroche J, Cluzel P, Toledano D, Montalescot G, Touitou D, Grenier PA, et al. Images in cardiovascular medicine. Cardiac involvement

in Erdheim–Chester disease: magnetic resonance and computed tomographic scan imaging in a monocentric series of 37 patients. Circulation 2009;119(25):e597–8.
[32] Hervier B, Arnaud L, Charlotte F, Wechsler B, Piette JC, Amoura Z, et al. Treatment of Erdheim–Chester disease with long-term high-dose interferon-α. Semin Arthritis Rheum 2012;41(6):907–13.
[33] Rahman MT, Nakayama K, Rahman M, Katagiri H, Katagiri A, Ishibashi T, et al. KRAS and MAPK1 gene amplification in Type II ovarian carcinomas. Int J Mol Sci 2013;14(7):13748–62.
[34] Madureira P, de Mello RA. BRAF and MEK gene rearrangements in melanoma: implications for targeted therapy. Mol Diagn Ther 2014;18(3):285–91.
[35] Andrulis M, Lehners N, Capper D, Penzel R, Heining C, Huellein J, et al. Targeting the BRAF V600E mutation in multiple myeloma. Cancer Discov 2013;3(8):862–9.
[36] Michaloglou C, Vredeveld LC, Soengas MS, Denoyelle C, Kuilman T, van der Horst CM, et al. BRAFE600-associated senescence-like cell cycle arrest of human naevi. Nature 2005;436(7051):720–4.
[37] Kriegl L, Neumann J, Vieth M, Greten FR, Reu S, Jung A, et al. Up and downregulation of p16(Ink4a) expression in BRAF-mutated polyps/adenomas indicates a senescence barrier in the serrated route to colon cancer. Mod Pathol 2011;24(7):1015–22.
[38] Acosta JC, Banito A, Wuestefeld T, Georgilis A, Janich P, Morton JP, et al. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nat Cell Biol 2013;15(8):978–90.
[39] Diamond EL, Abdel-Wahab O, Pentsova E, Borsu L, Chiu A, Teruya-Feldstein J, et al. Detection of an NRAS mutation in Erdheim–Chester disease. Blood 2013;122(6):10.
[40] Aitken SJ, Presneau N, Tirabosco R, Amary MF, O'Donnell P, Flanagan AM. An NRAS mutation in a case of Erdheim Chester disease. Histopathology 2015;66(2):316–9.
[41] Emile JF, Diamond EL, Hélias-Rodzewicz Z, Cohen-Aubart F, Charlotte F, Hyman DM, et al. Recurrent RAS and PIK3CA mutations in Erdheim–Chester disease. Blood 2014;124(19):3016–9.
[42] Janku F, Vibat CR, Kosco K, Holley VR, Cabrilo G, Meric-Bernstam F, et al. BRAF V600E mutations in urine and plasma cell-free DNA from patients with Erdheim–Chester disease. Oncotarget 2014;5(11):3607–10.

Biography

Dr. Franco Silvestris was born in Bari, Italy in 1949. He was awarded with the M.D. degree in 1974 and with specializations in 'Clinical Hematology' and 'Oncology' in 1977 and 1980, respectively. Dr. Silvestris spent a four-years period in USA at the University of New Mexico, Albuquerque as Research Associate Professor by 1982 working on research collaborative projects in oncology with the University of Bari. By 1994 he completed a second period of studies over the University of Florida in Gainesville (USA) where he obtained a personal award for research in the autoimmunity field. Dr. Silvestris is Professor of 'Internal Medicine and Oncology' and Director of the School of Specialization in 'Oncology' at the University of Bari. Also, he heads a clinical division of Internal Medicine and Clinical Oncology at the Department of Internal Medicine and Oncology of the University of Bari.

At present, Dr. Silvestris is involved in a number of collaborative researches in oncology and particularly in studies of the pathogenesis of bone metastases in multiple myeloma and malignant lymphomas. In addition, he is also involved in other studies exploring the properties of mesenchymal stem cells in the regenerative medicine in human experimental models. His previous studies include specific fields of autoimmunity, immunodeficiencies and tumor immunology whose results have been widely published.

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