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Central Nervous System and Head and Neck Histiocytoses: A Comprehensive Review on the Spectrum of Imaging Findings

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Abstract

The histiocytoses are a rare group of varied but related disorders characterized by abnormal tissue proliferation of macrophages and dendritic cells within tissues. The purpose of this article was to review the imaging findings in patients presenting with CNS and with head and neck manifestations of these disorders. Histiocytoses include but are not limited to Rosai-Dorfman disease, Erdheim Chester disease, Langerhans cell histiocytosis, histiocytic sarcoma, and juvenile xanthogranuloma. A review of the literature was performed to determine the sites of disease involvement. This article includes the demographics, histopathologic criteria for diagnosis, and imaging features of these histiocytoses, and describes the manifestations in locations known to harbor disease: intraaxial and extra-axial intracranial regions, the calvaria, skull base, hypothalamopituitary axis, orbits, paranasal sinuses, spine, and the head and neck region. Histiocytoses have variable imaging appearances in the CNS and in the head and neck region, and radiologists should be aware of the spectrum of findings to avoid mistaking them for other disease processes.

Learning Objective—To understand the general pathophysiology, clinical presentation, and typical imaging characteristics of the most common histiocytoses; comprehend the morphologic and immunohistochemical characteristics of these histiocytoses and the hallmark findings on pathology; and be able to differentiate between these disorders based on their most common presentations.

INTRODUCTION

The histiocytoses are a collection of diseases that result from abnormal proliferation and deposition of histiocytes, a group of immune cells that form a part of the reticuloendothelial system. All histiocytes arise from common bone marrow precursor stem cells and are under the influence of various cytokines differentiate into monocytes, macrophages, and dendritic (antigen presenting) cells. Histiocytes play a role in both nonspecific defenses (innate

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immunity) and help initiate specific defense mechanisms (adaptive immunity) by phagocytizing pathogens and/or cellular debris and by presenting antigens to stimulate lymphocytes and other immune cells to augment response to pathogens.

Abnormal proliferation of histiocytes can occur at any step in cell differentiation and results in several distinct but related disorders. These disorders include Erdheim Chester disease (ECD), Rosai-Dorfman disease, Langerhans cell histiocytosis (LCH), histiocytic sarcoma, and juvenile xanthogranuloma. The histiocytoses are differentiated histopathologically through morphologic and immunohistochemical characteristics. The common feature in histiocytic lesions is proliferative, plump infiltrating cells that express CD68, a macrophage marker.¹⁻⁴ Some of these conditions are also accompanied by various degrees of tissue infiltration by other inflammatory cells.

Most of these disorders can affect multiple organ systems, each with varying predilection for the central nervous system (CNS) and the head and neck. This article reviewed these histiocytoses; highlighted their salient features, natural history, treatment options, key findings on histopathology; and, finally, illustrated the imaging patterns of CNS as well as head and neck involvement. A table that summarizes the key clinical and radiographic features of these diseases has been provided (Table 1).

TYPES OF HISTIOCYTOSES

ECD

ECD, first described in 1930 by Jacob Erdheim and William Chester is a rare non-Langerhans cell type histiocytosis that usually affects men more than women in their fifth to seventh decade of life.^{5,6} ECD has a predilection for the appendicular skeleton. Imaging in these cases reveals bilateral symmetric long bone osteosclerosis. Extrasosseous manifestations are varied and often involve the retroperitoneum, mediastinum, pulmonary interstitium, and the skin.^{5,7}

Neurologic and maxillofacial involvement occurs in <50% of cases and affects the hypothalamopituitary axis, brain parenchyma, orbits, and paranasal sinuses.^{5,8} Meningeal thickening (which mimics meningiomas) and vertebral involvement are less common CNS manifestations. Other manifestations include involvement of the venous sinuses, choroid plexus, calvaria, and periarterial infiltration.^{5,8} Patients with CNS involvement most commonly present with diabetes insipidus, panhypopituitarism, exophthalmos, papilledema, and ataxia.

Often, patients are asymptomatic, and ECD is diagnosed incidentally when imaging is performed for other reasons.⁶ The clinical course of ECD is unpredictable. Although some patients never develop symptoms, others rapidly decline and die of renal failure, cardiomyopathy, or pulmonary fibrosis related to progressive involvement of these organs.⁶ Various treatments, including steroids, chemotherapy, radiation, and immune therapy, have, unfortunately, demonstrated little benefit in patients with progressive disease.⁹

Histopathologic Diagnosis—ECD shows foamy histiocytes in a fibrotic background. Minimal infiltration by mixed inflammatory cells, lymphocytes, plasma cells, and/or eosinophils may be present. The histiocytes in this process are negative for CD1a, although they may show S100 staining by immunohistochemical evaluation (Fig 1).

Rosai-Dorfman Disease

The initial disease was described by Destombes in 1965, and later defined by Rosai and Dorfman.^{4,10} Rosai-Dorfman disease, or the less preferred term, sinus histiocytosis with massive lymphadenopathy, is a benign phagocytic-type histiocytosis that presents in children and young adults, with a slight African and male predominance.⁴ Most patients (95%) present with cervical lymphadenopathy, whereas abnormal lymph nodes can also be present in the axilla or inguinal regions.^{4,10} Extranodal involvement is seen in approximately half of the patients. Clinical symptoms include blood lymphocytosis, fever, night sweats, and weight loss.¹¹

Head and neck involvement is common; however, CNS involvement is rare.¹¹ Most common sites of extranodal head and neck disease include the skin, sinonasal cavity, salivary and lacrimal glands, orbits, and bone.¹¹ CNS manifestations include meningeal thickening (at times mimicking meningioma), with possible involvement of the dural venous sinuses, cranial nerves, arteries, and the hypothalamopituitary axis.⁴ Clinical outcome of this disease depends on the site of involvement. Clinical observation is recommended unless compression on, or compromise of, major vital organs is noted, wherein surgical debulking is preferred to immune suppression, chemotherapy, or radiation.⁴ The prognosis is generally quite good.⁴

Histopathologic Diagnosis—Rosai-Dorfman disease demonstrates massive sheets of plump histiocytes that may fill lymph nodes or soft tissue. The abundant pink cytoplasm surrounds small round nuclei that often show engulfed inflammatory and red blood cells (termed emperipolesis), which remain intact within the cytoplasm of the histiocyte. These histiocytes are positive for CD68 and S100 and lack CD1a (Fig 2).

LCH

LCH is a rare disease, which occurs in approximately 0.2–2.0 cases per 100,000 children <15 years of age.¹² LCH, the most common and characterized of the histiocytoses, represents a disease with uninhibited Langerhans cells, a bone marrow–derived cell of the dendritic line. The disease predominately presents in young children, with a peak age of 1–3 years, and with a male predilection.¹³ Almost any organ may be affected.¹² LCH is generally divided into 3 categories: single organ involvement with single lesion (the historic name is eosinophilic granuloma), which has the best prognosis; single organ involvement with multiple lesions (Hand-Schueller-Christian disease), which has an intermediate prognosis; and multiple organ involvement with multiple lesions (Letterer-Siwe disease), which has the worst prognosis.¹³ These categories, however, are indistinguishable on pathology. Clinical presentation includes non-specific symptoms, such as fever; lethargy; weakness; weight loss; and, in depending on the organ of involvement, bone pain, skin

ulcers, anemia, and lymphadenopathy; and symptoms related to endocrine dysfunction can be found.¹⁴

Involvement of the hypothalamopituitary axis is the most common intracranial manifestation, which affects 10% of patients, who often present with diabetes insipidus.¹⁵ Patients with pituitary involvement can also present with deficiency of one or more anterior pituitary hormones or panhypopituitarism. Other, less common, CNS sites include the calvaria (presents as sharply marginated lytic bone lesion), meninges, choroid plexus, pineal gland, white matter, and cerebellum (presents with cerebellar degeneration).¹⁵ Within the spinal column, LCH classically presents as a vertebra plana deformity. Treatment depends on the site and the manifestation of disease. Solitary bone lesions are treated by surgical resection and have the best prognosis. Widespread disease is treated with a combination of surgery, chemotherapy, and radiation that is tailored to the individual patient.¹⁵

Histopathologic Diagnosis—LCH demonstrates CD1a⁺ cells and also may express S100. Clonality of these cells has been, on a molecular level, theorized to represent cellular activation, followed by proliferation. The histiocytes form relatively uniform sheets and are accompanied by marked eosinophilic inflammatory infiltrate. The nuclei are reniform, with a central groove (“coffee bean nuclei”). By electron microscopy, “tennis-racket” shaped cytoplasmic organisms, known as Birbeck granules, characterize this process (Fig 3).

Histiocytic Sarcoma

Histiocytic sarcoma is an extremely rare disorder, with only a few hundred cases reported in the medical literature. The median age at diagnosis is 46 years, with a slight male predilection.¹⁶ In the past, histiocytic sarcoma has often been misdiagnosed as lymphoma.³ The most common sites of disease involvement include the intestinal tract, skin, soft tissues, and lymph nodes; however, any organ may be involved.³ Involvement of the CNS is rare, usually presenting as leptomeningeal infiltration.¹⁷ Brain parenchymal, spinal cord, and peripheral nerve involvement have also been reported.¹⁷ Overall prognosis is poor, and the mainstay of treatment is chemotherapy.¹⁶ This disease is in contradistinction to “malignant fibrous histiocytoma,” which is a soft-tissue sarcoma.¹⁸

Histopathologic Diagnosis—Histiocytic sarcoma is a malignant form of histiocytic tumors and is described by growth patterns that present microscopically within the tumor, including storiform-pleomorphic, myxoid, giant cell, and inflammatory types, which show a predominance of xanthoma cells (lipid-containing histiocytes). Immunohistochemical evaluation, in general, is not helpful and is used predominately to exclude other tumor types. Mitoses are often easily identified (Fig 4).

Juvenile Xanthogranuloma

Juvenile xanthogranuloma, first described by Adamson in 1905, is a rare, usually self-limiting, histiocytic disorder of young children, most often presenting with cutaneous involvement of the head, neck, and trunk, which may be present at birth.¹⁹ The median age at diagnosis is 2 years with a male to female ratio of 1.5:1 in infancy.¹⁹ Although the most common manifestation is a single dermal nodule, multiple nodules can be seen and tend to

occur in infancy.¹⁹ Extracutaneous and/or organ involvement is rare and, when seen, most commonly involves the orbit.^{19,20} Brain parenchymal lesions have been reported with juvenile xanthogranuloma.¹⁹ Skin lesions generally follow a benign course, with spontaneous resolution. Extracutaneous lesions, especially intracranial lesions, can be associated with a higher morbidity.^{21,22} Fair-to-good response with steroids, surgery, radiation, and chemotherapy has been reported.^{20,21}

Histopathologic Diagnosis—Juvenile xanthogranuloma lesions contain cellular infiltrates composed of mononuclear cells (histiocytes) and Touton giant cells (nuclei that form a ringlike pattern) (Fig 5).

DISEASE MANIFESTATIONS AND IMAGING FINDINGS

CNS, as well as head and neck involvement, is encountered in this group of disorders, with a wide variety of imaging manifestations, depending on the location of disease occurrence.

Supratentorial Extra-Axial Lesions

Supratentorial extra-axial involvement in ECD, Rosai-Dorfman disease, and LCH is seen as dural thickening or dural-based masses (Fig 6). Although most cases of intracranial Rosai-Dorfman disease present with concomitant cervical nodal disease, several case reports illustrated extra-axial involvement as the sole site of disease, where such lesions may be mistaken for meningiomas.⁴ The dural-based lesions are usually isointense to gray matter on T1- and T2-weighted imaging and demonstrate avid contrast enhancement.¹⁰ Sedrak et al⁶ described nonenhancing (Fig 6B), T2-hyperintense spicules radiating outward from the center of the mass in ECD. Although extra-axial histiocytotic lesions may demonstrate a dural tail and enhancement, hemorrhage, calcifications, bony erosion, or hyperostosis is not seen.^{4,10} The persistence of delayed hyperenhancement within these lesions, even several days after gadolinium administration, has also been reported.⁴ Other lesions in the differential diagnoses include nerve sheath tumors and dural metastases.

Supratentorial Intra-Axial Lesions

Supratentorial, intra-axial involvement is rare in all types of histiocytoses and usually manifests collectively with other more common locations. Intra-axial mass lesions have been reported in both ECD and LCH.^{6,15} Sedrak et al⁶ described linear extension from the ependymal surface of the lateral ventricle to the basal ganglia (Fig 7). T1 signal intensity hyperintensity in the basal ganglia and mixed T2 signal intensity in the globus pallidus have also been described.^{8,23} Key differential diagnoses would include primary brain tumors, such as ependymomas and gliomas; lymphoma; and metastatic disease. Infectious processes would also be in the differential diagnosis.

Infratentorial Intra-Axial Lesions

Lesions in the infratentorial brain may involve the cerebellum or brain stem. ECD in the cerebellum has been described to have no mass effect (Fig 8A), possibly from loss of the myelin sheath with associated gliosis.²⁴ Enhancing lesions in the pons may be nodular or irregularly shaped, usually oriented transversely across the pons (Fig 8B, -C).^{6,8,25} T2

FLAIR signal hyperintensity in the pons and dentate nucleus may be diffuse, present in a microvascular pattern or as patchiness.^{6,12,26} Cerebellar atrophy may also occur, especially in LCH.¹² Differential diagnostic considerations include brain stem or cerebellar gliomas, lymphoma, and metastatic disease.

Lesions of the Hypothalamopituitary Axis

Involvement of the hypothalamopituitary axis is a fairly common intracranial manifestation of the histiocytoses and may present as thickening of the infundibulum >3 mm (Fig 9A) or as a nodular enhancing T2-hyperintense mass (Fig 9B).^{6,12,25} Disease may also extend into the hypothalamus (Fig 9A, -C) or the cavernous sinus (Fig 9C).⁶ The hallmark clinical finding of involvement of the pituitary stalk is diabetes insipidus. Differential diagnoses would include pituitary adenomas, germinomas, hypothalamic glioma, lymphoma, metastasis, infection, eosinophilic granuloma, and sarcoidosis.

Lesions of the Cavernous Sinus

Lesions that involve the cavernous sinuses have been reported to occur as disease extending from the sella (Fig 9C) or the pericarotid region.^{6,8,27} The signal intensity and enhancement characteristics are similar to the lesion that involves the sella or the pericarotid region, with visible direct extension.⁶ In addition, irregular expansion of the cavernous sinus is usually present.⁶ Nonhistiocytotic pituitary lesions described above are included in the differential diagnosis for cavernous lesions. If only expansion of the cavernous sinus is noted, without an enhancing mass-lesion, then a cavernous-carotid fistula should be included in the differential diagnosis.

Lesions of the Orbits

Ophthalmic manifestations are rare, seen in approximately 10% of patients. Disease may occur as an enhancing, T2-hyperintense intraconal orbital mass that appears to arise from the optic nerve sheath.²⁷ Imaging findings may range from subtle perineural infiltration (Fig 6A) to large homogeneous mass lesions (Fig 10).^{4,23,27} Disease can also occur in the eyelids and lacrimal glands (Fig 11). Involvement of the bones of the orbit may occur in LCH, with extension through the superior orbital fissure.^{26,28,29} The eye is a frequent site of extracutaneous involvement with juvenile xanthogranuloma.²⁰ Differential considerations would include optic gliomas, metastatic disease, nerve sheath tumors, and lymphoma.

Lesions of the Calvaria and Maxillofacial Bones

Bony involvement of the maxillofacial region and bones of the orbit is a classic presentation seen in LCH^{28,29} and may include sharply demarcated lytic lesions, with bone destruction, tumorous soft-tissue infiltration, and intracranial extension (Fig 12). Bony involvement in the non-LCH histiocytoses is less common (Fig 13). Differential diagnosis would include myeloma, fibrous dysplasia, and lytic metastases.

Lesions of the Paranasal Sinuses

Disease of the paranasal sinuses are nonspecific and may present as inflammatory processes, including polypoid thickening or soft-tissue opacification of the sinuses (Fig 14), which can

be T2 hyperintense and demonstrate contrast enhancement.⁴ Lesions of the calvaria and bones of the maxillofacial region may also extend into the paranasal sinuses.^{6,8} Primary sinonasal tumors, pseudotumor secondary to reactive mucosal polypoid thickening, and metastatic disease are in the differential diagnosis.

Lesions of the Vertebral Column and Spine

The histiocytoses may involve the vertebral column either as focal lesions (Fig 15A) or as diffusely infiltrative processes.^{6,30} LCH classically presents within the bony spine as a vertebra plana deformity, typically seen in the pediatric population. Lesions may also occur within the spinal canal (Fig 15B) and appear similar to spinal meningiomas (Fig 15C).²⁶ Differential diagnosis would include metastatic disease that either involves the bony spine or the dura, in addition to meningiomas, benign, and malignant nerve sheath tumors.

Neck Soft Tissues

Patients with Rosai-Dorfman disease most often present with bilateral cervical adenopathy, which occurs in up to 80% of patients.¹¹ Adenopathy can also be seen in LCH but is less common in ECD. The enlarged lymph nodes are T2 hyperintense and generally demonstrate avid contrast enhancement with areas of necrosis. Cervical adenopathy is similar to lymphoma, underlying infection or metastatic disease. Juvenile xanthogranuloma has been reported to occur as a mass in the neck and tongue (Fig 16) and mimics head and neck malignancies.^{19,31}

CONCLUSION

The histiocytoses may involve the brain and spine as well as the head and neck. Although these are rare diseases, knowledge of the clinical and imaging presentations of these histiocytoses allows radiologists to be mindful of these diseases and suggest them in the differential diagnosis in the setting of atypical presentation of common lesions. Doing so will alert the neuropathologists to screen for the appropriate markers and establish diagnosis, which thus allows for the implementation of appropriate therapy.

ABBREVIATION KEY

CNS	central nervous system
ECD	Erdheim Chester disease
LCH	Langerhans cell histiocytosis

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Fig. 1.
ECD, H&E stained tissue section (magnification 100×). Monotonous foamy histiocytes are scattered in a fibrotic background in ECD.

Fig. 2. Rosai-Dorfman disease, H&E stained tissue section (magnification 100×). Rosai-Dorfman disease, showing sheets of plump histiocytes with prominent engulfing of inflammatory cells (emperipolesis), which remain intact and are identified within the histiocytic cytoplasm (arrows).

Fig. 3.
LCH, H&E stained tissue section (magnification 100×). LCH is composed of slightly elongated histiocytes with nuclear grooves in a sea of eosinophils. Immunohistochemical evaluation for CD1a highlights the abnormal histiocytes in LCH.

Fig. 4. Histiocytic sarcoma, H&E stained tissue section (magnification 100×). The tumor cells are in sheets with numerous mitotic figures. By immunohistochemical evaluation, the neoplastic cells are positive for CD68 and S100, and negative for CD1a (not shown).

Fig. 5. Juvenile xanthogranuloma, H&E stained tissue section (magnification 100×). A nasal lesion from a 3-year-old with juvenile xanthogranuloma shows squamous epithelium with underlying cellular infiltrate composed of mononuclear cells (histiocytes) and Touton giant cells (the nuclei form ringlike pattern) (*arrow*).

Fig. 6. Supratentorial, extra-axial location. (A) A 50-year-old man with Rosai-Dorfman disease. Axial T1 postcontrast MR imaging shows multiple homogeneously enhancing extra-axial masses along the cerebral convexities and the skull base (*large arrows*). The right optic nerve sheath is also involved (*small arrows*) (B) A 48-year-old woman with ECD. Axial T1 postcontrast MR imaging with multiple enhancing dural-based masses (*large arrows*), with hypointense spicules radiating outward from the center of each mass (*small arrows*).

Fig. 7. Supratentorial, intra-axial location. A 60-year-old man with ECD. Coronal T1 postcontrast MR imaging shows ependymal involvement, with extension to the right basal ganglia (*arrows*). This enhancement resolved after treatment with interferon.

Fig. 8.

Infratentorial, intra-axial location. (A) A 14-year-old boy with Rosai-Dorfman disease. Axial T1 postcontrast MR imaging demonstrates an enhancing intra-axial lesion within the right cerebellar hemisphere without mass effect. (B, C) A 60-year-old man with ECD. Axial T1 postcontrast and axial FLAIR MR imaging demonstrates enhancement and FLAIR hyperintensity oriented in a transverse pattern across the pons.

Fig. 9.

Hypothalamopituitary axis. (A) An 8-year-old girl with LCH. Coronal T1 postcontrast MR imaging demonstrates involvement of the pituitary stalk and hypothalamus (*arrow*). (B) A 53-year-old man with Rosai-Dorfman disease. Sagittal T1 postcontrast MR imaging illustrates disease in the sella and suprasellar region (*arrow*). (C) The same patient as in (B), coronal T1 postcontrast MR imaging with extension to involve the hypothalamus (*large arrows*) and laterally into the cavernous sinuses (*small arrows*).

Fig. 10. Orbits. A 47-year-old man with ECD. Axial T1 postcontrast MR imaging with disease that involves the retrobulbar orbit (*large arrows*), with extension through the superior orbital fissure and posteriorly into the cavernous sinuses (*small arrows*).

Fig. 11.

Eyelids and lacrimal glands. A 53-year-old woman with juvenile xanthogranuloma. Coronal T1 postcontrast MR imaging shows disease that involves the left eyelid, lacrimal gland, and periorbital soft tissues (*large arrows*). Disease is also present in the sinonasal cavity and the right lacrimal gland (*small arrows*).

Fig. 12. Calvaria. A 10-year-old boy with LCH. (A) Plain radiographs show a lytic frontal calvarial lesion (*arrow*). (B) Coronal T1 postcontrast MR imaging demonstrates a calvarial mass with intracranial extension and involvement of the adjacent dura (*arrow*).

Fig. 13. Skull base. A 8-year-old girl with LCH. Axial T1 postcontrast MR imaging demonstrates involvement of the sphenoid bone and left temporal calvaria (*large arrows*), with extension into the orbits (*small arrows*).

Fig. 14. Paranasal sinuses. A 63-year-old woman with Rosai-Dorfman disease. Axial T1 postcontrast MR imaging shows disease filling the maxillary sinuses (*arrows*).

Fig. 15.

Spine. A 56-year-old woman with Rosai-Dorfman disease. (A) Axial T1 postcontrast MR imaging shows involvement of the T9 vertebral body and paraspinal soft tissues (*large arrows*), with associated epidural disease (*arrow*). (B) A 53-year-old man with Rosai-Dorfman disease. Coronal T1 postcontrast MR imaging with involvement of the spinal canal (*arrows*), extending off the sella and clivus. (C) The same patient as in (B); axial T1 postcontrast MR imaging demonstrates an extra-axial mass with a similar appearance to a meningioma.

Fig. 16. Soft-tissue neck. A 30-year-old woman with histiocytic sarcoma. (A) Sagittal T1 postcontrast MR imaging, with a lesion that involves the base of the tongue (*arrows*). (B) Axial contrast-enhanced CT demonstrates recurrent disease (*large arrows*) after laryngectomy and flap reconstruction (*small arrows*).

Table 1

Summary of Key Features of the CNS and Head and Neck Histiocytosis

Histiocytosis type	ECD	Rosai Dorfman disease	LCH	Histiocytic sarcoma	Juvenile xanthogranuloma
Demographics	M >> F; age, 50–70 y	M > F; children and young adults, African race	Pediatric population	M > F; rare, middle age adults	Infants and toddlers; may be present at birth
Clinical manifestation	Often asymptomatic; patients with CNS involvement can present with diabetes insipidus, panhypopituitarism, exophthalmos, papilledema, and ataxia	Lymphocytosis, fever, night sweats, and weight loss	Nonspecific symptoms, such as fever, lethargy, weakness, weight loss, and, depending on the organ of involvement, bone pain, skin ulcers, anemia, lymphadenopathy, and diabetes insipidus	Similar presentation as lymphoma	Single or multiple dermal nodules that involve the head, neck, and trunk
Key imaging findings	Bilateral symmetric long bone osteosclerosis, within the CNS can present as meningioma; can also manifest with renal, pulmonary, or cardiac involvement	Bilateral cervical lymphadenopathy, within the CNS can mimic meningioma	Lytic calvarial lesions, vertebra plana, cerebellar degeneration, hypothalamopituitary axis involvement	Leptomeningeal disease	Head and neck manifestation is rare, can present as tongue or neck mass
Prognosis	Unpredictable clinical course, some patients develop rapidly progressive disease that leads to death, whereas others remain asymptomatic throughout their lives	Generally good	Depends on the degree of involvement; single organ involvement has the best prognosis	Poor	Skin involvement only, self-limiting disease, excellent prognosis; head and neck involvement; good to fair prognosis

Note:—F indicates female; M, male.