Cancer Association of South Africa (CANSA)

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Fact Sheet
on
Lymphomatoid Granulomatosis

Introduction

Lymphomatoid granulomatosis (LG or LYG) is a very rare lymphoproliferative disorder characterised in 1972 with 'lymphomatoid' meaning lymphoma-like and 'granulomatosis' denoting one of its microscopic characteristics, polymorphic lymphoid infiltrates and focal necrosis (tissue death) within it.

[Picture Credit: LG]

While most commonly found in middle age patients, it has been observed in young people with a study identifying 47 cases of patients aged 0–18 years in the literature. It is said that males are found to be affected twice as often as females. (Wikipedia).

Lymphomatoid Granulomatosis (LG)

Lymphomatoid granulomatosis (LG), also known as angiocentric lymphoma orangiocentric immunoproliferative lesion, is a rare type of non-Hodgkin's lymphoma (Radiopedia).

Synonyms of Lymphomatoid Granulomatosis:

- benign lymph angiitis and granulomatosis
- malignant lymph angiitis and granulomatosis
- pulmonary angiitis
- pulmonary Wegener's granulomatosis

Lymphomatoid granulomatosis is a rare disorder characterised by overproduction (proliferation) of white blood cells called lymphocytes (lymphoproliferative disorder). The abnormal cells infiltrate and accumulate (form lesions or nodules) within tissues. The lesions or nodules damage or destroy the blood vessels within these tissues. The lungs are most commonly affected in lymphomatoid granulomatosis.

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Symptoms often include cough, shortness of breath (dyspnoea) and chest tightness. Other areas of the body such as the skin, kidneys or central nervous system are also frequently affected.

The abnormal cells in lymphomatoid granulomatosis are B-cells (B lymphocytes) containing the Epstein-Barr virus. There are two main types of lymphocytes: B-lymphocytes, which may produce specific antibodies to 'neutralise' certain invading microorganisms, and T-lymphocytes, which may directly destroy microorganisms or assist in the activities of other lymphocytes.

Because lymphomatoid granulomatosis is caused by the overproduction of abnormal B-cells, affected individuals may eventually develop B-cell lymphoma, a form of non-Hodgkin's lymphoma. Lymphoma is a general term for cancer of the lymphatic system.
(National Organization for Rare Disorders).

Incidence of Lymphomatoid Granulomatosis (LG) in South Africa
The National Cancer Registry (2012) does not provide information on Lymphomatoid Granulomatosis (LG). It is a form of non-Hodgkin's Lymphoma.

According to the National Cancer Registry of 2012, the following number of Non-Hodgkin's Lymphoma cases was histologically diagnosed in South Africa during 2012:

Group - Males 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	933	1:206	2,53%
Asian males	29	1:222	3,39%
Black males	555	1:274	4,76%
Coloured males	79	1:212	1,81%
White males	271	1:121	1,35%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	797	1:311	2,12%
Asian females	21	1:333	1,96%
Black females	500	1:401	3,03%
Coloured females	70	1:272	1,68%
White females	206	1:179	1,30%

The frequency of histologically diagnosed cases of Non-Hodgkin's Lymphoma in South Africa for 2012 was as follows (National Cancer Registry, 2012):

Group - Males 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	32	46	134	208	199	146	105	49
Asian males	1	0	2	4	7	5	5	2
Black males	24	33	108	158	127	53	22	9
Coloured males	3	5	9	12	18	12	11	6
White males	4	8	12	30	44	74	62	31

Group - Females 2012	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	17	50	144	188	141	106	92	44
Asian females	0	0	2	4	6	3	4	0
Black females	11	39	120	156	81	37	27	10
Coloured females	2	3	8	14	9	13	14	6
White females	4	8	13	12	43	49	47	26

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Signs and Symptoms of Lymphomatoid Granulomatosis (LG)

The list of signs and symptoms mentioned in various sources for LG includes the 27 symptoms listed below:

- Premature death 70% die within 5 years of onset
- Persistent rhinitis
- Malaise
- Fever
- Cough
- Severe weight loss
- Coughing up blood
- Seizures
- Hypertension (high blood pressure)
- Breathing difficulty
- Chest pain
- Diarrhoea
- Joint Pains Muscle pain (myalgia)
- Discoloured skin spots
- Skin nodules
- Skin ulcers
- Respiratory distress
- Ulcerative lesion
- Nasal obstruction (blocked nose)
- Nose bleeds (epistaxis)
- Death of surrounding tissue (necrosis)
- Destruction of surrounding tissue
- Stuffy nose
- Nasal pain
- Perforated nasal septum
- Destruction of facial tissue

(Right Diagnosis).

Diagnosis of Lymphomatoid Granulomatosis (LG)

The differential diagnosis of the clinical and radiological manifestations of lymphomatoid granulomatosis (LG) is extensive and beyond the scope of this article. When tissue is available for histology, the following 2 groups of diseases need to be differentiated from lymphomatoid granulomatosis:

- Other types of pulmonary granulomatosis
  - Bronchocentric granulomatosis and Churg-Strauss (allergic angiitis and granulomatosis) are characterized by asthma and eosinophilia, which are not features of lymphomatoid granulomatosis.

- Necrotising sarcoid granulomatosis has nodular pulmonary sarcoid lesions that mimic lymphomatoid granulomatosis. Unlike lymphomatoid granulomatosis, in necrotizing sarcoid, mediastinal adenopathy often occurs; extrapulmonary disease rarely exists; and histology demonstrating well-formed granulomas with central necrosis also exists.
- WG, unlike angiitis seen in lymphomatoid granulomatosis, is a true vasculitis with acute and chronic inflammatory cells and vessel destruction. Sinus, upper airway, and renal involvement with necrotizing glomerulonephritis are common in WG but rare in lymphomatoid granulomatosis.

- Other types of malignant lymphoma
  - Hodgkin disease is different because pulmonary involvement without mediastinal adenopathy is rare. The diagnosis requires demonstration of Reed-Sternberg cells.
  - Nasal angiocentric lymphoma (NAL), also known as polymorphic reticulosis or lethal midline granuloma, and lymphomatoid granulomatosis initially were believed to be the same disease, with the former predominantly affecting the upper airway. Recent work has shown that NAL is an EBV-related, natural killer (NK) cell lymphoma and a separate disease entity. Lymphomatoid granulomatosis does not affect the upper airway and nasal passages.
  - Non-Hodgkin lymphoma has well-described pulmonary and extranodal involvement. In particular, peripheral T-cell lymphomas are characterized by vascular infiltration and a degree of morphological heterogeneity. Careful histological diagnosis and studies to determine clonal expansion of T cells are required to rule out lymphomatoid granulomatosis.

(Medsape).

Treatment of Lymphomatoid Granulomatosis (LG)

The most effective therapy for individuals with lymphomatoid granulomatosis is unknown. For individuals with minimal disease, observation may be recommended since long-term survival without treatment has occurred as well as spontaneous remission. In most cases, however, treatment is recommended. Treatment recommendations are mostly based on the grade of disease. Lymphomatoid granulomatosis is pathologically divided into three grades (I, II, III), which are determined by the number of EBV+ B-cells and the extent of necrosis. In patients with grade I/II disease, interferon alfa-2b has been shown to be highly effective in most patients, and leads to longterm remissions and potential cures. In patients with grade III disease, interferon alfa-2b is not effective, and combination chemothearpy with rituximab should be used. However, there is a frequent rate of recurrence with grade I/II disease following chemotherpy-rituximab in grade III disease.

Corticosteroids alone are only recommended as a temporizing measure and should not be used for long term control of lymphomatoid granulomatosis. Similarly, rituximab alone is seldom effective for long term control. Neither of these agents effectively eradicates and abnormal EBV clones and corticosteroids can increase immusuppression and ultimately disease progression.

If patients develop lymphomatoid granulomatosis on immune suppressive agents, they should be stopped if possible and the patient observed. If the disease is progressive or advanced, then treatment as outlined above should be instituted.
(National Organization for Rare Disorders).

The therapeutic approach and optimal management have not been well defined. In several studies, therapy has ranged from observation to treatment with prednisone or chemotherapy. In the largest reported study of 152 patients, no significant difference in mortality or disease-free survival was found in treatment options, and the mortality rate exceeded 50%. New therapeutic approaches are necessary. In view of the association of lymphomatoid granulomatosis (LYG) with EBV and the similarity to posttransplant lymphoma, the use of antiviral drugs with minimal immunosuppressive therapy is advocated.

- Patients with a benign course require no treatment. Spontaneous remission has been reported.
- Corticosteroids, with or without chemotherapy, may be recommended.
  - Treat symptomatic or progressive disease.
  - In general, therapy involves prednisone with antineoplastic agents (eg, cyclophosphamide).
  - More than 50% of patients with lymphomatoid granulomatosis respond to treatment.
  - Recurrence is usual and may include refractory disease or progression to high-grade lymphoma (13-47%).
  - When lymphomatoid granulomatosis progresses to high-grade lymphoma, combination antilymphoma regimens are used, but response rates are poor at this stage.
- Localised disease may respond to radiotherapy.
- Surgical resection of isolated pulmonary masses followed by chemotherapy has been associated with disease-free survival for at least 2 years.
- Other treatment options include ganciclovir, interferon alfa-2, or, depending on histologic grade, combination chemotherapy.

(Medscape).

Prognosis (Outlook)

The median survival from diagnosis is 14 months. More than 60% of patients die within 5 years. The cause of death is usually extensive destruction of the pulmonary parenchyma, resulting in respiratory failure, sepsis, and, occasionally, massive haemoptysis (coughing up of blood). Poor prognostic indicators include an age younger than 30 years, neurological or hepatic involvement, leukopenia or pancytopenia, and anergy (absence of the normal immune response to a particular antigen or allergen).
(Medsacpe).

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