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Distinguishing benign mediastinal masses from malignancy in a histoplasmosis-endemic region

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Abstract

Objective—To describe the characteristics of benign and malignant mediastinal masses, which may predict their etiology and facilitate the safe and timely management of patients, especially those residing in histoplasmosis-endemic regions.

Study design—We conducted a retrospective review of the health records of 131 patients aged <19 years who were referred to two tertiary care children's hospitals from 2005-2010 for the evaluation of mediastinal masses.

Results—Most patients (79%) had benign masses, including 98 with confirmed or suspected histoplasmosis. Overall, patients with benign etiologies were younger, more likely to be African American, more likely to complain of cough and to have pulmonary nodules by chest computed tomographs than patients with cancer. Patients with malignant disease were more likely to complain of malaise and to have neck swelling, abnormal extrathoracic lymphadenopathy, lymphopenia, anterior mediastinal involvement and/or pleural effusion. Positive histoplasmosis serologic tests were specific but insensitive for a benign etiology. No single clinical, laboratory or radiologic feature was sufficiently sensitive and specific to distinguish between benign and malignant masses. For cancer, however, the presence of lymphopenia, anterior mediastinal involvement or enlarged cervical lymph nodes on computerized tomography had a sensitivity of 93%, specificity of 95%, positive predictive value of 86%, and negative predictive value of 97% for cancer. Sixty-four patients (49%) underwent invasive testing, including 37 (36%) of patients with benign masses.

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Conclusions—Patients in this series who had involvement of the anterior mediastinum, lymphopenia or enlarged cervical lymph nodes had a high likelihood of cancer. Expectant management of patients lacking these characteristics may be safe and reduce unnecessary invasive testing.

Keywords

tuberculosis; cancer; diagnosis

The incidence of mediastinal masses in the general population is estimated to be one case per 100,000 persons per year.[1] The differential diagnosis of these disorders is diverse. Malignant disease predominates in most series; neurogenic tumors, lymphomas and congenital abnormalities are common in children and lymphomas and germ cell tumors in young adults, but infections are important in some geographical areas.[2-9] Distinguishing between benign and malignant mediastinal masses is challenging for practitioners in areas endemic for histoplasmosis, where up to half of cases are attributable to this infection.[6, 7]

Despite its frequency, the presentation of mediastinal histoplasmosis in endemic regions has not been systematically characterized. The ability to distinguish malignant mediastinal masses from benign infections on the basis of clinical features or non-invasive testing would spare patients with benign diseases from unnecessary invasive procedures and allow those with malignancies, which may be rapidly progressive and life-threatening, to be identified at the earliest possible time. Past efforts to compare and contrast the presentation of benign and malignant mediastinal masses have found that no clinical, laboratory or radiological feature was sufficiently sensitive to distinguish these etiologies.[4, 5, 10] These studies have been relatively small or evaluated highly selected patient populations, and there have been advances in diagnostic microbiology and diagnostic imaging since these reports were published. We, therefore, sought to identify the characteristics that would be most useful in predicting final diagnosis by comparing the clinical, laboratory and radiographic features of a large group of children and adolescents with mediastinal masses residing in a geographic region that is highly endemic for histoplasmosis.

Methods

St. Jude Children's Research Hospital (St. Jude) provides comprehensive care to children with cancer and other catastrophic illnesses. Le Bonheur Children's Hospital is the major pediatric tertiary care hospital and teaching facility for the University of Tennessee Health Sciences Center (UTHSC). Together, these institutions provide all secondary and tertiary care for children and adolescents in the Memphis, TN, metropolitan and surrounding areas. Patients evaluated for mediastinal masses at these hospitals between January 1, 2005 and December 31, 2010 were identified using ICD-9 codes for histoplasmosis (115.0-9), malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs (165.0, 165.8), intrathoracic lymph nodes (196.1), benign neoplasms of respiratory and intrathoracic organs (212.3, 212.5) and swelling, mass or lump in chest (786.6). Patients <19 years of age (inpatients and outpatients) who resided in a zip code included in the hospitals' local primary and secondary catchment areas were included.

Demographic characteristics, signs and symptoms at the time of presentation, laboratory and radiographic findings at the time of Infectious Diseases evaluation were abstracted from health records. The institutional review boards of UTHSC and St. Jude approved this study with waiver of consent.

Benign masses were defined as those for which cancer was definitively excluded by tissue biopsy or that did not have cancer etiology established, and failed to progress over a prolonged period of observation. Confirmed cases of histoplasmosis had either: (1) *Histoplasma capsulatum* isolated from blood or tissue; (2) histopathologic staining of tissue biopsies revealing granulomas and yeast forms; and/or (3) specific diagnostic tests suggesting histoplasmosis [a complement fixation titer of ≥1:8 for yeast (CF-Y) or mycelia (CF-M), positive immunodiffusion assay (ID) or *H. capsulatum* antigen detected in urine or serum].[11] Although a single CF titer of >1:32 generally is regarded as suggestive of acute histoplasmosis, a lower titer was considered suggestive in this study because up to one-third of cases may have titers of 1:8 or 1:16.[11] Probable histoplasmosis cases did not meet the criteria listed above for proven histoplasmosis, had negative tests for tuberculosis and had no other specific alternative diagnosis established. Diagnostic tests for other infectious and rheumatologic causes of mediastinal masses were obtained at providers' discretion. Hematologic and biochemical test results were considered abnormal if they fell outside of the institutional age-related range of values. Neutropenia and lymphopenia were defined as <1000 cells/mm^3.

Ann Arbor staging system “B” symptoms included unexplained fevers, drenching night sweats or greater than 10% unintentional weight loss in the preceding 6 months.[12] Other symptoms (anorexia, headache, cough, dyspnea, chest pain, neck swelling and malaise) were recorded as being reported by the patient on history. If there was any mention of palpably enlarged lymph nodes in the cervical, supraclavicular, axillary or inguinal regions by a physician, patients were classified as having palpable abnormal extrathoracic lymphadenopathy. The presence of neck swelling on physical examination, reported separately from cervical lymphadenopathy, also was recorded. Auscultatory findings such as crackles, reduced air entry and wheeze were noted.

Results of computed tomography (CT) of the chest were extracted from diagnostic radiology reports. Mediastinal masses were characterized as being in the anterior, middle or posterior mediastinum according to the radiologist's interpretation. Extrathoracic lymphadenopathy included enlarged lymph nodes in one or more of the following regions: cervical, supraclavicular, axillary and retroperitoneal.

Statistical Analyses

Categorical values were compared using Chi-square or Fisher exact tests. Continuous variables were expressed as mean ± SD or median and range. *P* values <0.05 (2-tailed test) were considered statistically significant. Univariable and multivariable logistic regression was performed to determine the association of independent variables with etiology, and odds ratios (OR) and 95% confidence intervals (CI) reported. Variables with $P \leq 0.1$ in univariate analyses were included in final models. Sensitivity, specificity, positive and negative

predictive values were determined for individual and combinations of predictors. The incidence of mediastinal masses in this region was calculated using the 2010 census population of children for the defined catchment area. Statistical analysis was performed using Stata 9.0.

Results

Overall, 131 patients with intrathoracic masses were identified (average 5.3/100,000 persons <19 years of age per year). Subjects were followed for a median of 3.4 months (range 0-75.5 months). Most masses (104, 79%) were benign (Table I). Malignant masses (n=27) included Hodgkin lymphoma (n=14), non-Hodgkin lymphoma [n=12; precursor T-lymphoblastic lymphoma (n=7), diffuse large B-cell lymphoma (n=3), Burkitt lymphoma (n=1)] and desmoid tumor (n=1). Most patients with benign masses had confirmed (n=67, 51%) or probable (n=31, 24%) histoplasmosis. Other benign disorders included unspecified lymphadenopathy (n=2), and nonspecific lymphadenitis, benign cysts, benign hyalinized nodule and ganglioneuroma (n=1 each). No patient had definite tuberculosis; three children were treated for presumed tuberculosis because of positive skin tests but had persistent mediastinal adenopathy after completing therapy; their mediastinal masses were attributed to histoplasmosis. Few patients had diagnostic testing for other infectious and non-infectious causes of mediastinal masses; no patient was reported to have a specific alternative diagnosis at the time of their last follow-up evaluation. The demographic, clinical and laboratory characteristics of patients with confirmed histoplasmosis were similar to those with probable histoplasmosis except those with confirmed infection were more likely to report fever (45% vs. 22%, p=0.03).

Patients with benign masses were significantly younger than those with malignant masses (11.3 years versus 13.6 years, p=0.02; Table I). Most patients (66%) were African American; the racial distributions of patients with benign and malignant masses were significantly different (p=0.009; Table I). When controlled for other demographic factors, both age (OR for each year increase in age 0.87, 95% CI 0.78-0.98, p=0.02) and race (OR 3.06, 95% CI 1.32-7.11, p=0.009) remained significantly associated with a benign mass.

The most common presenting symptoms of patients were cough, fever and chest pain (Table I). “B” symptoms were more commonly reported by patients with malignancies. Cough and chest pain were more frequent in patients with benign masses, whereas patient-reported malaise and neck swelling were more common in malignant disorders. In a multivariable analysis, cough (OR 4.01, 95% CI 1.21-13.31, p=0.02) was associated with an increased risk, whereas, the complaint of neck swelling (OR 0.05, 95% CI 0.01-0.27, P<0.001) and malaise (OR 0.14, 95% CI 0.04-0.44, P=0.001) were associated with a reduced risk of a benign mass.

Overall, 87% patients had normal physical examinations; this was more common in patients with benign than malignant conditions (88 vs. 21%, p<0.001; Table I). No respiratory signs were associated with type of mass. Abnormal extrathoracic adenopathy (67% in malignant versus 13% in benign masses, p<0.001) and health care providers' observation of neck swelling (30% in malignant versus 3% in benign masses, p<0.001) were more common in

patients with malignant masses. Both abnormal extrathoracic lymphadenopathy (OR 0.09, 95% CI 0.03-0.24, p<0.001) and neck swelling (OR 0.03, 95% CI 0.01-0.11, p<0.001) remained significantly associated with a benign mass on multivariate analysis.

Laboratory test

The white blood cell counts of patients with benign and malignant disease were similar (Table II). Leukocytosis and anemia were equally common, few patients were neutropenic and none was thrombocytopenic. Those with benign masses had lower mean absolute neutrophil counts, higher mean absolute lymphocyte counts (ALC) and lower mean platelet counts (Table II) than patients with cancer; only patients with malignancies were lymphopenic (37% versus 0%, p<0.001). There were no significant differences in renal function or serum hepatic enzymes. Although patients with benign conditions were less likely to have elevated serum uric acid (UA) and more likely to have elevated serum lactate dehydrogenase concentrations, these differences were not statistically significant. When controlled for other laboratory abnormalities, only higher mean ALC (OR 1.002, 95% CI 1.0006-1.003, P=0.003) and absence of lymphopenia (OR infinite, p<0.001) remained significantly associated with benign disease.

Elevated serum antibodies to both *Histoplasma* yeast and mycelial antigens were more commonly detected in patients with benign masses than those with cancer (Table III) but only 44% of patients with malignant masses underwent serologic testing. Most patients with positive CF-Y [42/45 (no./No.), 93%] and CF-M serology [7/9, 78%] had titers of ≥1:32. *Histoplasma* antigen was detected in the urine of 2 of 28 (5%) patients with benign masses; no other specific diagnostic tests yielded useful information.

Diagnostic imaging

There were 117 (89%) patients with chest CT results available (Table IV). Most (n=96, 82%) had masses limited to a single mediastinal compartment. Exclusive involvement of the middle mediastinum, pulmonary nodules and mediastinal node calcification were more common in benign disease, whereas any anterior mediastinal involvement, any extrathoracic lymphadenopathy and pleural effusions were more common in patients with cancer. Splenic lesions were observed only in patients with benign disease and retroperitoneal adenopathy only in patients with cancer. When controlled for other radiologic abnormalities, the presence of pulmonary nodules (OR 7.91, 95% CI 1.43-43.70, P=0.018), and the absence of anterior mediastinal mass (OR 0.03, 95% CI 0.01-0.15, p<0.001), pleural effusion (OR 0.11, 95% CI 0.01-0.79, p=0.028) or extrathoracic lymphadenopathy (OR 0.08, 95% CI 0.02-0.43, P=0.003) remained significantly associated with benign disease.

Patient management

Sixty-four patients (49%), including 37/104 (36%) patients with benign masses, underwent invasive diagnostic testing (e.g. CT-guided or open biopsy) to establish a diagnosis. Invasive testing was more likely in patients with an anterior mediastinal mass, pleural effusion, night sweats, malaise, neck swelling by history or physical examination, abnormal lymphadenopathy on examination, and in older patients and those who received initial care at St. Jude. Patients with positive serologic tests for histoplasmosis, pulmonary nodules and

isolated middle mediastinal involvement were more likely to be managed expectantly. In a multivariable analysis, any abnormal extrathoracic lymphadenopathy on examination (OR 8.89, 95% CI 2.82-28.09, p<0.001), anterior mediastinal involvement (OR infinite, p<0.001) and exclusive involvement of the middle mediastinum (OR 0.31, 95% CI 0.13-0.77, p=0.012) were independently associated with invasive diagnostic testing. No complications of these procedures were reported.

Clinical prediction rule

Patients with mediastinal masses often are evaluated by infectious diseases specialists and oncologists with results from preliminary diagnostic tests and CT scans before the results of specific tests for infectious diseases are available or when these tests are negative. Therefore we sought to identify characteristics that would distinguish children with malignant disease from those with benign disorders at the earliest opportunity. In this, we considered that some clinical features (eg, malaise) are subjective and may be prone to recall bias. Others (e.g. retroperitoneal adenopathy) have a low prevalence or are not routinely evaluated. A history of neck swelling or healthcare providers' observation of neck swelling, lymphopenia, the presence of abnormal cervical, supraclavicular or axillary lymphadenopathy on CT scan, an anterior mediastinal mass and the absence of a middle mediastinal mass were each >95% specific for malignancy but, individually, identified only 11-81% of malignant disease. The presence of lymphopenia, anterior mediastinal involvement or abnormal cervical adenopathy on CT, however, had a sensitivity of 93%, specificity of 95%, positive predictive value (PPV) of 86% and negative predictive value (NPV) of 97%. Including other factors did not improve sensitivity or specificity.

As results of serologic testing frequently are not available at the initial assessment, we determined the effect of adding these results to the clinical prediction rule to determine if knowledge of these results improved the accuracy of clinical prediction. A positive CF-Y test had a sensitivity of 63%, specificity of 100%, PPV of 100% and NPV of 85% for benign disease; a positive CF-M test was less sensitive and immunodiffusion was both less sensitive and specific. Having both a middle mediastinal mass and positive CF-Y tests had a sensitivity of 61%, specificity of 100%, PPV of 100% and NPV of 75%. Having exclusively middle mediastinal involvement and a positive CF-Y test had a sensitivity of 54%, specificity of 100%, PPV of 100% and NPV of 25%.

Discussion

The incidence of mediastinal masses in the current study was >5-fold higher than previous estimates; confirmed and probable histoplasmosis accounted for 75% of disease.[1, 13] Irrespective of etiology, most patients came to attention because of with respiratory and systemic symptoms and middle mediastinal masses. Clinical characteristics proved less useful in distinguishing benign from malignant disease than the results of diagnostic imaging and laboratory tests. Notably, because these were common in both benign and malignant disease, “B” symptoms, elevated uric acid level, and the absence of pulmonary nodules or calcification, characteristics considered by many practitioners to be suggestive of malignancy, discriminated poorly between groups. Cough was more common in patients

with benign masses, perhaps reflecting the inflammatory nature of granulomatous disease and the greater likelihood of airway compression with middle mediastinal masses.[13] Abnormal cervical or supraclavicular lymphadenopathy was frequently evident on CT in patients with cancer, even when not apparent on physical examination; this or the subclinical obstruction of thoracic venous return probably accounted for the increased incidence of neck swelling in this group. Of note, significantly more patients with malignancies complained specifically of malaise, although this was infrequently reported.

The greater risk of malignancy in older children probably reflects the increasing incidence of lymphoma, whereas individual's risk of histoplasmosis is more dependent on environmental exposure than age.[14] Mediastinal masses, particularly benign masses, were more common in African American than in Caucasian patients than would be expected for the demographic composition of the Memphis metropolitan area (63% black, 29% white) and Shelby County (53% black, 43% white).[15] Although non-Hodgkin lymphoma is more common in whites than blacks and genetic differences in susceptibility to histoplasmosis have been reported, these factors are unlikely to account for a difference of this magnitude.[16, 17] Residential areas in the Memphis metropolitan area had racial dissimilarity indices of 32-66% over the study period suggesting that, as previous studies have illustrated, differences in exposure or the intensity of exposure to infectious conidia in the environment at the neighborhood level might contribute to higher rates of histoplasmosis in some racial and ethnic groups.[16, 18]

Lymphopenia that is unrelated to cytotoxic chemotherapy has been described in patients with solid tumors and hematologic malignancies.[19] The action of lymphocytotoxic cytokines and/or bone metastases may be responsible. Notably, few patients in this series had significant nutritional deficiencies that might also affect lymphocyte counts.

Our data are consistent with that of Gaebler et al, who, in a study of 37 children in a *Histoplasma* endemic region in the early 1980s, found that 67% of children with histoplasmosis had a CF titer of ≥1:32 and a middle mediastinal mass, whereas none with lymphoma had these features.[5] A relatively high specificity of *Histoplasma* serology in distinguishing *Histoplasma* infections from malignant causes of mediastinal masses also was noted by Weinberg et al.[20] Firm conclusions about the utility of serologic testing in the management of mediastinal masses are limited because few patients with cancer in this series had these tests obtained. None of the 9 patients with malignancy tested had a positive CF antibody test (0%, 95% CI 0-34%), but one (11%, 95% CI 0-45%) had a positive immunodiffusion antibody test. Positive CF antibody titers, therefore, might be given greater weight in management decisions, but a larger prospective study is needed. Middle mediastinal masses were more common in patients with benign than malignant disease in the current study. Having both a positive CF titer and middle mediastinal mass was reassuring for a benign etiology (specificity of 100%), but the sensitivity of this combination of features was only 61%. *Histoplasma* antigen detection was insensitive compared with serologic tests. This is likely due, at least in part, to relatively rapid declines in antigenemia and antigenuria following acute infection. [11]

Had the clinical prediction rule been applied to the study population, two patients with malignancy would have been misclassified, a 9 yr-old with T-cell lymphoblastic lymphoma

with a middle mediastinal mass and large pleural effusion and a 5-year old with a posterior mediastinal desmoid tumor. Four of the 70 patients with benign masses who had results of both CBC and chest CT available would have been misclassified. All presented with both anterior and middle mediastinal involvement; one had abnormal cervical and axillary adenopathy identified on chest CT. Three of these patients had serologic tests for histoplasmosis obtained; these were positive in two cases.

In total, 37 children who would have been classified as being at low risk for malignancy using the clinical prediction rule underwent invasive diagnostic testing, including 16 with negative tests for histoplasmosis. Analysis of the characteristics of patients who underwent invasive diagnostic testing suggests that healthcare providers understand, consciously or unconsciously, that abnormal lymphadenopathy is a risk factor for malignant disease, but the significance of lymphopenia may not have been appreciated. The compartmentalization of mediastinal masses often is cited as being helpful in distinguishing between malignant and benign masses, with malignancies more likely to involve the anterior mediastinum.[3, 21, 22] Our data are consistent with this observation, although exclusive involvement of the anterior mediastinum by malignant disease may be less common than previously appreciated.[21]

This study has several limitations. Some older adolescents might have received care at adult healthcare facilities. Diagnostic tests were not obtained uniformly in all subjects. Few patients with malignant disease had histoplasmosis serologic testing, perhaps because providers assumed that positive tests might be common in endemic regions or an undesirable delay in results was anticipated. Histoplasmosis and cancer might have co-existed in some patients, as previously reported.[10] As with any retrospective study, our results may have been influenced by recall, reporting and information bias. It will be important to validate our findings prospectively and in geographic areas where the epidemiology of mediastinal masses differs from the current study.

This study contributes to our understanding of the demographic, clinical, laboratory and radiologic features of mediastinal masses in histoplasmosis-endemic regions and identifies characteristics that differentiate between benign and malignant etiologies. Patients in this series who had involvement of the anterior mediastinum, lymphopenia or abnormal adenopathy had a high likelihood of cancer, but expectant management of those lacking these characteristics, especially those who also have positive CF tests for histoplasmosis, may be safe and reduce unnecessary invasive testing.

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Abbreviations

Ab	antibody
Ag	antigen
ALC	absolute lymphocyte count
ALT	serum alanine aminotransferase concentration
ANC	absolute neutrophil count
AST	serum aspartate aminotransferase concentration
CF	complement fixation
CI	confidence interval
Cr	serum creatinine concentration
CT	computed tomography
ESR	erythrocyte sedimentation rate
CRP	C-reactive protein
ID	immunodiffusion
ID-M	histoplasma mycelial antibody by immunodiffusion
ID-Y	histoplasma yeast antibody by immunodiffusion
LDH	serum lactate dehydrogenase
NPV	negative predictive value
OR	odds ratio
PPV	positive predictive value
St. Jude	St. Jude Children's Research Hospital
UA	serum uric acid
UTHSC	University of Tennessee Health Sciences Center
WBC	white blood count

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Table 1

Demographics and clinical features of patients with mediastinal masses, according to final diagnosis

	Total (N=131)	Benign (N=104)	Malignant (N=27)	Unadjusted OR (95% CI)	P
Mean age, years	11.7 (4.5)	11.3 (4.5)	13.6 (4.2)	0.87 (0.78-0.98)	0.021
Male sex	68 (52)	52 (50)	16 (59)	1.45 (0.62-3.43)	0.39
Race				3.06 (1.32-7.11)	0.009
African American	90 (70)	78 (76)	14 (52)		
Caucasian	33 (26)	19 (19)	23 (45)		
Asian	1 (1)	1 (1)	0 (0)		
Other	5 (4)	4 (4)	1 (4)		
Symptoms					
Fever*	53 (41)	40 (39)	13 (48)	0.68 (0.29-1.60)	0.38
Night sweats*	24 (18)	13 (13)	11 (41)	0.21 (0.08-0.55)	0.001
Weight loss*	29 (22)	17 (17)	12 (44)	0.25 (0.10-0.62)	0.003
Any “B” symptom*	66 (51)	47 (46)	19 (70)	0.35 (0.14-0.88)	0.025
Cough	66 (51)	58 (56)	8 (30)	3.06 (1.22-7.62)	0.016
Dyspnea	27 (21)	21 (20)	6 (22)	0.90 (0.32 -2.50)	0.83
Chest pain	44 (34)	39 (38)	5 (19)	2.68 (0.94-7.66)	0.07
Any respiratory symptom	90 (69)	78 (76)	12 (44)	3.90 (1.61-9.43)	0.003
Neck swelling	13 (10)	3 (3)	10 (37)	0.05 (0.01-0.20)	<0.001
Malaise	26 (20)	14 (14)	12 (44)	0.20 (0.08-0.51)	0.001
Physical signs					
Cervical lymphadenopathy	26 (21)	12 (12)	14 (52)	0.13 (0.05-0.34)	<0.001
Axillary adenopathy	10 (8)	2 (2)	2 (7)	0.05 (0.01-0.25)	<0.001
Inguinal adenopathy	4 (3)	2 (2)	5 (10)	0.26 (0.04-1.96)	0.19
Supraclavicular adenopathy	3 (2)	2 (2)	1 (4)	0.55 (0.05-6.28)	0.63
Any extrathoracic adenopathy	31 (25)	13 (13)	18 (67)	0.08 (0.03-0.21)	<0.001

	Total (N=131)	Benign (N=104)	Malignant (N=27)	Unadjusted OR (95% CI)	P
Pulmonary signs**	11 (9)	8 (8)	3 (11)	0.72 (0.18-2.92)	0.65
Neck swelling	11 (9)	3 (3)	8 (30)	0.07 (0.02- 0.30)	<0.001

Data are presented as mean (SD) and No. (%)

Abbreviation: B symptoms, fever and/or night sweats and/or unintentional weight loss

*B symptoms include fever, night sweats and involuntary weight loss

**Pulmonary signs include decreased air entry, crepitations and wheezes

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Table 2

Diagnostic laboratory test results of patients with mediastinal masses, according to final diagnosis

	Overall (N=131)	Benign (N=104)	Malignant (N=27)	Univariable OR (95% CI)	Univariable *P* value
Mean WBC/mm^3	10,067 (6,082)	9,898 (6,320)	10,622 (5,306)	0.98 (0.92-1.05)	0.59
Mean ANC/mm^3	5,984 (4,270)	5,380 (3,924)	7,932 (4,810)	1.00 (1.00-1.00)	0.010
Leukocytosis*	34/111† (31)	24/84 (29)	10/34 (37)	0.68 (0.27-1.70)	0.41
Neutropenia**	3/108 (3)	3/81 (4)	0/27 (0)	∞	0.57
Mean ALC/mm^3	2,425 (1,370)	2,678 (1,354)	1,609 (1,090)	1.00 (1.00-1.00)	<0.001
Lymphopenia**	10/108 (9)	0/81 (0)	10/27 (37)	0.00	<0.001
Mean Hct (g/dL)	35.6 (5.2)	35.6 (4.8)	35.37 (6.2)	1.01 (0.93-1.10)	0.75
Anemia	69/110 (63)	48/83 (58)	21/27 (78)	0.39 (0.14-1.07)	0.07
Mean platelet count (×10^3/mm^3) Thrombocytosis	389 (136)	371 (123)	436 (165)	1.00 (0.99-1.00)	0.04
Thrombocytosis	39/109 (36)	27/83 (33)	12/26 (46)	0.56 (0.23-1.38)	0.21
Thrombocytopenia	0/109 (0)	0/83 (0)	0/26 (0)	0.00	
Mean LDH (U/L)	434 (264)	458 (278)	385 (231)	1.00 (1.00-1.00)	0.24
Elevated LDH	44/80 (55)	32/53 (60)	12/27 (44)	1.90 (0.75-4.86)	0.18
Mean uric acid (mg/dL)	4.3 (1.5)	4.0 (1.1)	4.7 (2.1)	0.75 (0.54-1.04)	0.09
Elevated UA	4/73 (5)	1/46 (2)	3/27 (11)	0.18 (0.02-1.80)	0.14
Mean ESR (mm/hr)	50 (35)	47 (34)	56 (39)	0.99 (0.98-1.01)	0.45
Elevated ESR	38/51 (75)	27/37 (73)	11/14 (79)	0.74 (0.17-3.20)	0.68
Mean CRP (mg/dL)	7.8 (10.0)	7.7 (10.8)	8.2 (6.9)	64 (0.27-11.00)	0.61
Elevated CRP	50/57 (88)	37/43 (86)	13/14 (93)	0.47 (0.05-4.32)	0.51

Data are presented as mean (SD) and No. (%)

* Determination of low or high values based on age-related limits at the two institutions with the exception of ANC and ALC defined below

** Neutropenia and lymphopenia defined as <1000 cells/mcl

† no./No.

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; ALT, serum alanine aminotransferase concentration; AST, serum aspartate aminotransferase concentration; Cr, serum creatinine concentration; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LDH, serum lactate dehydrogenase; UA, serum uric acid; WBC, white blood count

Table 3

Results of serologic and microbiologic tests for histoplasmosis of patients with mediastinal masses, according to final diagnosis

	Overall (%)	Benign (%)	Malignant (%)	Unadjusted OR (95% CI)	P
Ab CF-Y	45/81* (56)	45/72 (63)	0/9 (0)	∞	<0.001
Ab CF-M	9/79 (11)	9/70 (13)	0/9 (0)	∞	0.59
ID-M band	34/71 (48)	33/62 (53)	1/9 (11)	9.10 (1.07-77.21)	0.04
ID-H band	10/71 (14)	10/62 (16)	0/9 (0)	∞	0.34
Any positive serology	64/96 (67)	63/87 (72)	1/9 (52)	21.00 (2.49- 176.95)	0.005
Positive urine Ag	2/47 (4)	2/41 (5)	0/6 (0)	∞	1.00
Positive blood Ag	0/32 (0)	0/23 (0)	0/9 (0)	0	1.00
Positive blood culture	0/35 (0)	0/27 (0)	0/7 (0)	0	1.00
Any positive test	66/108 (61)	65/68 (68)	1/12 (8)	23.06 (2.85-186.72)	0.003

* no./No.

Data are presented as No. (%)

Abbreviations: Ag, *H. capsulatum* antigen; Ab CF-M, histoplasma mycelial antibody by complement fixation; Ab CF-Y, histoplasma yeast antibody by complement fixation; ID-M, histoplasma mycelial antibody by immunodiffusion; ID-Y, histoplasma yeast antibody by immunodiffusion

Table 4

Diagnostic imaging results of patients with mediastinal masses, according to final diagnosis

	Overall (N=117)	Benign (N=93)	Malignant (N=24)	Unadjusted OR (95% CI)	P
Anterior mediastinal mass	24 (21)	4 (4)	20 (74)	0.02 (0.00-0.06)	<0.001
Anterior mediastinal involvement only	4 (3)	1 (1)	3 (11)	0.08 (0.01-0.84)	0.04
Middle mediastinal mass	111 (95)	87 (97)	24 (89)	3.63 (0.69-19.12)	0.13
Middle mediastinal involvement only	86 (69)	80 (82)	6 (22)	16.47 (5.78-46.95)	<0.001
Posterior mediastinal mass	6 (5)	3 (3)	3 (11)	0.28 (0.05-1.46)	0.13
Posterior mediastinal involvement only	2 (2)	2 (2)	0 (0)		1.00
Pulmonary nodules	62 (53)	57 (63)	5 (19)	7.60 (2.63-21.97)	<0.001
Any parenchymal disease (including pulmonary nodules)	71 (61)	62 (69)	9 (33)	4.43 (1.77-11.07)	0.001
Cervical adenopathy	12 (10)	1 (1)	11 (41)	0.02 (0.00-0.14)	<0.001
Supraclavicular adenopathy	14 (12)	3 (3)	11 (41)	0.05 (0.01-0.20)	<0.001
Axillary adenopathy	9 (8)	3 (3)	6 (22)	0.12 (0.03-0.52)	0.005
Any extrathoracic adenopathy	23 (20)	6 (7)	17 (63)	0.04 (0.01-0.13)	<0.001
Retroperitoneal adenopathy	6 (5)	0 (0)	6 (22)	0	<0.001
Splenic involvement	4 (3)	4 (4)	0 (0)	∞	0.57
Intraabdominal involvement	10 (9)	4 (4)	6 (22)	0.16 (0.04-0.63)	0.009
Pleural effusion	17 (15)	6 (7)	11 (41)	0.10 (0.03-0.32)	<0.001
Pericardial effusion	11 (9)	9 (10)	2 (7)	1.39 (0.28-6.85)	0.69
Calcified pulmonary nodules	10 (9)	8 (9)	2 (7)	1.21 (0.24-6.12)	0.81
Calcified mediastinal adenopathy	27 (23)	24 (27)	3 (11)	2.91 (0.80-10.55)	0.10

Data are presented as No. (%).