Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials.

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Running head :

Prognostic clinico-pathological features of angioimmunoblastic T-cell lymphoma

This study has been accepted as a poster presentation at the XIII meeting of the European Association for Haematopathology (Vienna, october 2006) and as an oral presentation at the 48th meeting of the American Society of Hematology (Orlando, december 2006)

Key Words

Angioimmunoblastic T-cell lymphoma, treatment, clinical, biological and histological prognostic factors

Abstract

Purpose: to evaluate the prognostic significance of clinical, biological and pathological features in angioimmunoblastic T-cell lymphoma (AITL).

Methods: 157 patients with AITL were retrieved from the GELA LNH87 and LNH93 trials. 147 patients received an anthracycline-based polychemotherapy. Histologically, 41 cases were classified as “rich in large cells” (> 10% T and/or B blasts) and 116 as “classic” (including 19 rich in epithelioid cells, 14 rich in clear cells, and 4 with hyperplastic germinal centers). 62 cases were evaluated for CD10 and CXCL13 expression and scored according to the abundance of positive lymphoid cells.

Results: there was a male predominance. Median age was 62 years. 81%, 50% and 67% of patients had an advanced stage, a non ambulatory performance status and an IPI>2 respectively. Anemia, hypergammaglobulinemia, and elevated LDH level were observed in 65%, 50% and 66% of patients respectively. CD10 and CXCL13 were considered to be positive in atypical lymphoid cells, in 71% and 73% of cases respectively. With a median follow-up of 69 months, the 5y overall survival was 33%. In multivariate analysis, male gender (p=0.002), age ≤ 60y (p=0.008), mediastinal involvement (p=0.017) and anemia (p=0.021) were poor prognostic indicators for overall survival. IPI and PIT scores were not predictive of survival. Overall, “classic” and “rich in large cells” AITL subgroups were not different regarding clinical presentation and outcome.

Conclusion: our large series emphasizes the morphologic heterogeneity of AITL, and confirms the common expression of CXCL13 and CD10 markers. AITL carries a poor prognosis and few prognostic factors.

Introduction

Angioimmunoblastic T-cell lymphoma (AITL) represents a distinct clinicopathological entity, among nodal peripheral T-cell lymphomas (PTCL) (1). It generally occurs in elderly patients presenting with generalized lymphadenopathy, hepatosplenomegaly, anemia and hypergammaglobulinemia. Histological features of AITL include partial or complete effacement of the lymph node architecture by a polymorphous infiltrate that is typically associated with a proliferation of follicular dendritic cells (FDC) and a prominent arborization of high endothelial venules. The neoplastic cells are small to medium sized, display minimal cytological atypia and usually have a clear cytoplasm mostly in small clusters. They account for only a fraction of the infiltrate and are admixed with a reactive population of small lymphocytes, eosinophils, plasma cells, histiocytes and large lymphoid, sometimes Reed-Sternberg like B-cells which are often infected by Epstein-Barr virus (EBV) (2). AITL shows a morphological spectrum and increase in T-cell immunoblasts may be observed (1,3). Although it has not been thoroughly investigated, it was suggested that the increase in T-cell immunoblasts would indicate transformation into a peripheral T-cell lymphoma, unspecified (PTCL/U) (3). An increase in EBV-infected B-cells may also occur and in rare cases, an overt diffuse large B-cell lymphoma develops (4-6). The tumor cells usually express CD4, CD10, Bcl6 and CXCL13, a phenotype that is unique among T-cell lymphomas, suggesting their derivation from follicular helper T-cells (7-10).

AITL is rare accounting for about 2% of all non-Hodgkin lymphomas (11). There have been relatively little data concerning the impact of clinical, biological and morphological features of angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) and/or AITL on survival and outcome (12-18). In this report, we attempted to identify the prognostic significance of different pathological, biological and clinical parameters after a long follow-up of consecutive AITL patients treated with

chemotherapy according to LNH87 and LNH93 protocols conducted by the Groupe d'Etude des Lymphomes de l'Adulte (GELA). In particular, since rare cases of B-cell lymphomas have been reported to arise after AILD (4-5) and since it was suggested that the increase in T-cells could evolve into a PTCL/U (3), we intended to study the prognostic relevance of the increase (>10%) in large atypical cells, irrespective of their B or T-cell phenotype.

Patients and methods

Patient selection:

Eligibility criteria for this study included patients with confirmed diagnosis of AITL after histopathological and immunohistochemical review. The 157 AITL patients are a subset of 6700 patients enrolled in the LNH87 and LNH93 GELA trials for intermediate and high grade lymphomas. Part of the clinical features has been previously reported in 68 patients (19).

Histological analysis:

At the time of enrollment in the LNH87 and LNH93 protocols, lymph node biopsies were reviewed by pathologists of the GELA group and initially classified according to the Working Formulation (20) and updated Kiel classification (21), based on morphological examination of slides stained with hematoxylin-eosin and Giemsa and on immunohistochemistry comprising at least CD20 and CD3ε. For the purpose of the present study, four expert hematopathologists reviewed all T-cell lymphoma cases and completed the phenotype in order to reclassify them according to the WHO classification (1). In AITL cases, the diagnosis was based on the presence of the 5 following criteria: partial or diffuse effacement of the nodal architecture, vascular proliferation with prominent arborization of high endothelial venules,

extrafollicular meshwork of FDC, atypical population of CD3+ T cells, and large CD20+ B cells.

To uncover the prognostic significance of the increase in large cells, cases were assigned to 2 major categories: “rich in large cells” (> 10% large B and/or T cells) and “classic”, the latter including cases rich in clear cells, rich in epithelioid cells, and with hyperplastic germinal centers (fig 1A-1E).

Immunohistochemical analysis:

Immunohistochemistry was performed on deparaffinized tissue sections using an indirect immunoperoxidase method. After appropriate antigen retrieval, slides were stained for CD20, CD3ε and as far as possible CNA42 and/or CD21 antigens (DakoCytomation, Glostrup, Denmark). 36% of cases were tested for the presence of EBV using antibodies to latent membrane protein-1 (DakoCytomation) and/or in situ hybridization with probes specific for the EBV encoded small RNA (EBERs) sequences. Finally, 62 cases for which additional slides were available, were evaluated for CD10 (56C6; Novocastra, Newcastle, UK) and CXCL13 (R&D systems, Minneapolis, MN) expression and were assigned a score from 0 to 3 as follows (fig 1F-1H); 0: negative/ very few positive lymphoid cells; 1: scattered lymphoid positive cells with no or one occasional aggregate; 2: many scattered positive lymphoid cells with more than one aggregate; 3: sheets of positive lymphoid positive cells. For detection of CXCL13 expression, an amplification system was used as recently reported (10). Positive internal control included polymorphonuclear leucocytes and residual germinal center B cells for CD10 and FDC and follicular helper T-cells for CXCL13. Cases without positive internal control were excluded from the analysis.

Staging:

Patients were clinically staged according to the Ann Arbor classification. Initial investigations included a complete medical history and physical examination, computed tomography of the chest, abdomen and pelvis, bone marrow biopsy and biologic evaluation. Patients were randomized to treatment into one of the 4 groups of LNH87 and 7 groups of LNH93 protocols according to a score taking into account age and a number of prognostic factors of the age-adjusted International Prognostic Index (aaIPI) score (22). Patients were required to sign an informed consent approved by Hôpital Saint Louis, Paris- France institutional review board. They were excluded from the trial if they had positive serologic tests for HIV or HTLV1.

Treatment:

The results of both LNH87 and LNH93 protocols have in large part been published (23-31). Briefly, for younger patients, the reference arm was three to four courses of dose-intense doxorubicin, cyclophosphamide, vindesine, bleomycine, and prednisone (ACVBP) followed by sequential consolidation (76 patients) (31), and the experimental arm consisted of the following: eight cycles of methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone (mBACOD) in patients with no adverse factor (LNH 87-1, 11 patients) (23); four cycles of ACVBP-like with a second randomization between sequential consolidation and high-dose chemotherapy (CBV) with stem cell rescue for patients under 56 years with at least one adverse factor (LNH 87-2, 7 patients) (24); four alternating induction cycles of teniposide, ifosfamide, mitoxantrone, courses of etoposide, ifosfamide and mitoxantrone (VIM) and doxorubicin, cyclophosphamide, vindesine and methotrexate (ACVM) in patients between 56 and 69 years with at least one adverse factor (LNH 87-3, 14 patients) (25); three cycles of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) with involved field radiotherapy for patients with 0 aaIPI factors

(LNH 93-1, 2 patients) (26); four cycles of ACVBP-like followed by a modified consolidation for patients with 1 aaIPI factor (LNH 93-2, 2 patients); four cycles of ACVBP-like followed by high-dose chemotherapy with peripheral blood stem cell rescue for patients under 60 years with ≥ 2 factors (LNH 93-3, 17 patients) (27).

For elderly patients, the arms were: four cycles of CHOP with or without additional involved field radiotherapy for patients with 0 aaIPI factors (LNH 93-4, 3 patients) (28); eight cycles of CHOP or ACVBP for patients under 70 years with 1-3 aaIPI factors (LNH 93-5, 12 patients) (29); six cycles of CHOP like or reduced CHOP for patients ≥ 70 years and PS < 2 (LNH 87- 4 and LNH 93- 6, 11 patients) (30); oral chemotherapy with etoposide, chlorambucil, and prednisone for patients ≥ 70 years with a PS ≥ 2 (LNH 93-7, 2 patients).

Response to treatment was considered as complete (CR), unconfirmed complete (CRu), partial response or failure according to the International Workshop criteria (32).

Statistical analysis:

Patients' characteristics and remission rates were compared using chi-squared test. Event-free survival (EFS) was defined as the time interval between randomization to primary treatment failure, relapse and death from any cause or last follow-up. Overall survival (OS) was defined as the time interval between randomization to last follow-up or death from any cause. Estimates of survival were calculated according to the Kaplan-Meier method (33) and were compared using the log-rank test (34). Cox proportional-hazards regression analysis with OS and EFS as the dependent variables was used to detect potential independent prognostic factors. Differences were considered statistically significant when the two-sided p value was less than

0.05. All statistical analyses were performed using the Statistical Application System software (SAS, version 9, SAS institute, Cary, NC).

Results

Clinical and biological characteristics of AITL patients at presentation:

Between April 1987 and October 1999, 157 patients were included in the study. Table 1 summarizes their main clinical and biological characteristics. The median age was 62 years (range 20 to 89 years). Most patients (126/156; 81%) presented with an advanced stage III-IV and 21 % (29/139) had > 2 extranodal involved sites. Laboratory investigations showed the presence of anemia in 65% (101/155) of patients, a positive Coombs test in 33% (30/92), hypergammaglobulinemia >12g/l in 50% (73/146) and elevated serum LDH level in 66% (98/149). The international prognostic index (IPI) score was >1 in 89% (117/132) of patients and the prognostic index for PTCL/U (PIT) score (scoring system including age> 60y, performance status (PS) ≥ 2, LDH ≥ normal and bone marrow involvement) (35) was >2 in 39% (56/144).

Pathological findings:

By definition, all cases displayed FDC hyperplasia demonstrated by morphology and/or CNA42/CD21 immunostaining, as well as a variable proportion of CD20 large B cells within an atypical T-cell population. In addition, most of the tested cases disclosed EBV positive cells. According to their cytological aspect, 41 cases were classified as “rich in large cells” and 116 as “classic” (Table 2) including 19 rich in epithelioid cells, 14 rich in clear cells and 4 with hyperplastic germinal centers. Among the 62 cases interpretable for CD10 expression, 71% (n=52) disclosed aggregates or sheets of CD10 positive cells with atypical features (scored 2+3).

Scattered CD10 positive lymphoid cells (score 1) - the neoplastic nature of which could not be determined - were observed in 12% and CD10 was negative (score 0) in 17% of our cases. 45 out of 62 sections were adequate for CXCL13 interpretation. CXCL13 staining was found, as a dot reinforcement of the Golgi area, in aggregates or sheets of atypical cells (score 2+3) in 73% of cases, and in scattered lymphoid cells (score 1) in the remaining 27%. Overall, at least one marker was scored positive in 86% of the interpretable cases and both markers were negative in 14% of them.

Clinical outcome and prognostic parameters:

All but 10 patients received an anthracycline-based chemotherapy. CR/CRu was achieved in 46% of patients after induction therapy and 41% were in CR/CRu at the end of therapy. Overall, the two populations “classic” and “rich in large cells” were not statistically different in terms of clinical features, laboratory findings and treatment response (p=0.676) except for a higher frequency of elevated serum LDH (p=0.027) and β2 microglobulin levels (p=0.046) within the group “rich in large cells”. Furthermore, no difference could be observed between the different chemotherapeutic regimens, whether the treatment was considered intensive or not.

Follow-up could be assessed in 156 patients. The median follow-up was 68 months (3.77-161.47). The 2, 5 and 7-year OS rates were 51% (CI, 42.85-58.77), 33% (CI, 25.63-40.95) and 29% (CI, 21.19-36.73) respectively, fig (2A), reaching a plateau level around 6 years. The 2, 5 and 7-year EFS rates were 38% (CI, 30.66-46.06), 29% (CI, 21.54-36.02) and 23% (CI, 15.57-29.94) respectively, fig (2B). The distribution of OS and EFS curves was not statistically different between the groups, “classic” and “rich in large cells”, fig (3). In univariate analysis, male gender (p=0.004), mediastinal involvement (p=0.014) and anemia (p=0.048) were poor prognostic factors for OS (Table 1). Multivariate analysis (Table 3) showed that male

gender (p=0.002), age ≤ 60y (p=0.008), mediastinal involvement (p=0.017) and anemia (p=0.021) were independent prognostic factors for OS. OS differed significantly in favor of patients who developed CR/CRu (p<0.0001). IPI and PIT scores were not predictive of survival (fig 4). The different histological subtypes as well as CD10 and CXCL13 scoring did not have any influence on survival.

Discussion

In the present series of 157 AITL patients - the largest reported so far in which patients were included in randomized clinical trials - we further extend the peculiar clinical and biological findings of AITL and confirm its poor prognosis despite a first-line anthracycline-based chemotherapy with a curative intent in most patients. We also emphasize its morphologic heterogeneity as well as the common expression of CD10 and CXCL13 determined on routinely-fixed samples.

In keeping with previous reports (12-18, 36-38), we observed that AITL is a disease of the elderly presenting with systemic manifestations and features known to be poor prognostic factors for B-cell lymphomas: 54% of our patients were more than 60 years old, 50% had an altered PS, 81% presented with stage III-IV disease, 46% had more than one extranodal site involvement and 66% had an elevated LDH level. The clinical symptoms and biological signs are not specific of AITL but their association appears to be very suggestive of the disease. Notably, skin rash (44%), arthritis/arthralgia (16%), pleural effusion/ascites/edema (26%), hypergammaglobulinemia (50%) and positive Coombs test (33%) appear to represent distinctive manifestations of AITL.

A small number of studies sought to identify prognostic factors in AITL/AILD (12-18), yielding controversial results. Their results might be hampered by the relatively limited number of patients and/or the heterogeneous therapies including

prednisolone alone in a proportion of these patients. In the recent literature where the entity was considered as lymphoma, one study (15) found that survival was influenced by age, stage and number of symptoms including B symptoms, rash/pruritus, and LDH and hemoglobin levels, whereas other studies (16-18) found no reliable clinico-biological prognostic indicator for the disease. In the current study, where overall patients received more intensive chemotherapy compared to these previous reports, multivariate analysis showed that male gender (p=0.002), age ≤ 60y (p=0.008), mediastinal involvement (p=0.017) and anemia (p=0.021) were poor prognostic factors for OS. IPI, extensively used for B-cell lymphomas patients, has also been found to be of prognostic value in some PTCL series comprising AITL and other T-cell lymphomas entities (19, 39-41). In keeping with a previous study focusing on AITL (18), we found that IPI is not a significant predictor of survival (p=0.799). The prognostic model “PIT” proposed by Gallamini et al for PTCL/U was neither predictive of survival in the present series (p=0.106) (35). Moreover, in a previous study published by GELA (19), hypergammaglobulinemia > 20 g/l and eosinophilia ≥ $0.8x10^9$/l were more often encountered in AITL than in other subtypes of T-cell lymphomas. Overall, these data reinforce the idea that AITL is a distinct entity. Since IPI and hypergammaglobulinemia/ eosinophilia are supposed to reflect tumor load and immune dysregulation respectively, this may suggest that AITL related manifestations would more likely reflect immune dysregulation than tumor burden (7-9). The impact of the clinicopathological prognostic index (including age, LDH>normal, non ambulatory PS, Ki67 ≥ 80%) described by Went et al (42) for PTCL/U patients could not be assessed in our AITL series.

In the present series, we emphasize the morphologic heterogeneity of AITL, which could be a source of misdiagnosis to poorly experienced pathologists, especially

concerning cases with hyperplastic germinal centers and rich in epithelioid cells, the latter can be mistaken as Lennert's lymphoma or Hodgkin lymphoma. This is reflected by the large error rate (50%) in the referred cases described by Attygalle et al (7) and by our very low recruitment of cases with hyperplastic germinal centers, a pattern which has recently received attention since it was described in 1998 (43).

Few reports have tried to identify histological prognostic features, but none of them are of proven clinical value. Nathwani and colleagues (44) first noticed in 1978 that the presence of cohesive foci of immunoblasts in AILD, was associated with poorer outcome and more widespread disease at autopsy. More recently, Lee SS et al (18) identified two histological groups based on the absence or presence of large atypical T blasts or clusters of clear cells and found no statistical difference between these two groups in terms of clinical and laboratory findings and survival. The prognostic relevance of “the presence or absence” of clear cells was studied by two other groups (14,16) but their results are contradictory. We consider, however, the “mere presence” of clear cells to represent part of the morphologic features of AITL, and the “abundance” of clear cells did not influence survival in the present study (data not shown). The current study specially attempted to investigate the potential prognostic relevance for the increase in large cells, but it failed to show any significance on outcome for this increase. In this respect, the number of CD10 and CXCL13 positive atypical cells, which is supposed to represent the neoplastic counterpart, did not show any influence on survival.

It has been recently shown that CXCL13, a chemokine critically involved in B-cell migration into germinal centers, was highly up-regulated in the follicular T helper cell subset (45-47). Subsequently, we and others have shown that CXCL13 was expressed by neoplastic cells of most AITLs (9-10). CD10 and CXCL13 were proposed as sensitive immunohistochemical markers in AITL (7,9,10). This finding

was confirmed in the present study where at least one marker stained clusters of atypical lymphocytes in the majority (86%) of cases. However, in the few cases (14%) where it was difficult to assign the neoplastic nature for the rare scattered stained cells on pure morphological grounds, both markers were considered negative. In such circumstances, the diagnosis of AITL should rely on a combination of classical morphological criteria together with clinical and biological features.

Despite of various intensive regimens with an anthracycline-based chemotherapy, AITL, compared to other non-Hodgkin lymphomas, pursues an aggressive clinical course, so the optimal therapeutic regimen remains to be determined. AITL does not present any pertinent prognostic factor besides, naturally, the achievement of a complete response to therapy. However, after a long follow-up, we observed a trend for a plateau level reaching a survival probability of around 30% at 6 years. A longer follow-up is further needed to determine whether these patients are eventually cured of their disease.

Figure legends

Figure 1: Figures A to E illustrate angioimmunoblastic lymphoma sub-types: (A) “classic-type”, (B) “rich in large cells”, (C) with hyperplastic germinal centers, (D) rich in clear cells, (E) rich in epithelioid cells (hematoxylin eosin); Figures F to G illustrate CXCL13 immunostaining patterns, i.e. score 1 (F), score 2 (G) and score 3 (H) .

Figure 2: Overall survival (A) and event-free survival (B) of the 156 patients with angioimmunoblastic T-cell lymphoma.

Figure 3: Overall survival of patients with “classic” AITL compared to patients with AITL “rich in large cells”.

Figure 4: Overall survival of angioimmunoblastic T-cell lymphoma patients according to IPI (A) and PIT (B) scores.

Table 1: Clinico-biological characteristics of AITL patients and their relevance on overall survival

Table 2: Histopathologic and phenotypic characteristics of AITL patients and their correlation with overall survival (to be published online only)

Table 3: Parameters influencing survival of AITL patients in multivariate analysis

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Table 1

Characteristics	Number	Percentage	p value
Gender			0.004*
Male	95/157	60	
Female	62/157	40	
Age			0.072
Median	62		
Range	20-89		
≤60	72/157		
>60	85/157		
Performance status			0.721
0-1	79/157	50	
>1	78/157	50	
B symptoms	112/155	72	0.127
Ann Arbor Stage			0.426
I-II	30/156	19	
III-IV	126/156	81	
Bulky ≥10 cm	27/102	26	0.132
Number of extranodal sites			0.096
0-1	75/139	54	
>1	64/139	46	
Extranodal involvement			
Liver	38/154	25	0.132
Spleen	86/155	55	0.145
Mediastinum	86/153	56	0.014*
Skin	46/154	30	0.267
Lung	15/153	10	0.546
Bone marrow	71/151	47	0.775
Effusion/edema/ascites	16/62	26	0.895
Polyarthritis/arthralgia	12/76	16	0.810
Skin rash	36/82	44	0.598
IPI score			0.799
0-1	15/132	11	
2-3	67/132	51	
4-5	50/132	38	
PIT score			0.106
0-1	38/144	26	
2	50/144	35	
3-4	56/144	39	
Anemia (Hb ≤ 12g/dl)	101/155	65	0.048*
Positive Coombs test	30/92	33	0.300
Lymphopenia <= 700/µl	77/156	49	0.065
Thrombocytopenia ≤ 150/ µl	33/121	20	0.220
Hypereosinophilia > 500/ µl	12/38	32	0.373
Hypergammaglobulinemia >12g/l	73/146	50	0.260
Serum LDH level > normal	98/149	66	0.794
Hypoalbuminemia <35g/l	71/143	50	0.162
Serum β2 microglobulin level >3mg/l	71/107	66	0.911

AITL: angioimmunoblastic T-cell lymphoma
IPI: International prognostic index (age, performance status, stage, LDH)

PIT: Prognostic index for peripheral T-cell lymphoma, unspecified (age, performance status, bone marrow involvement, LDH)

Table 2 (to be published online only)

Pathological findings	Number	Percentage	p value
Classic	116	74	0.552
Rich in epithelioid cells	19	13	
Rich in clear cells	14	9	
With hyperplastic germinal	04	03	
Rich in large cells	41	26	
CD10	52		0.652
Score 0	09	17	
Score 1	06	12	
Score 2	25	48	
Score 3	12	23	
CXCL13	45		0.865
Score 0	0	0	
Score 1	12	27	
Score 2	24	53	
Score 3	09	20	

Table 3

Parameter	p	relative risk	95% CI low	95% CI high
Age ≤ 60y	0.008	1.712	1.150	2.549
Male gender	0.002	1.921	1.258	2.934
Anemia (Hb ≤ 12g/dl)	0.021	1.681	1.082	2.613
Mediastinal involvement	0.017	1.662	1.097	2.521

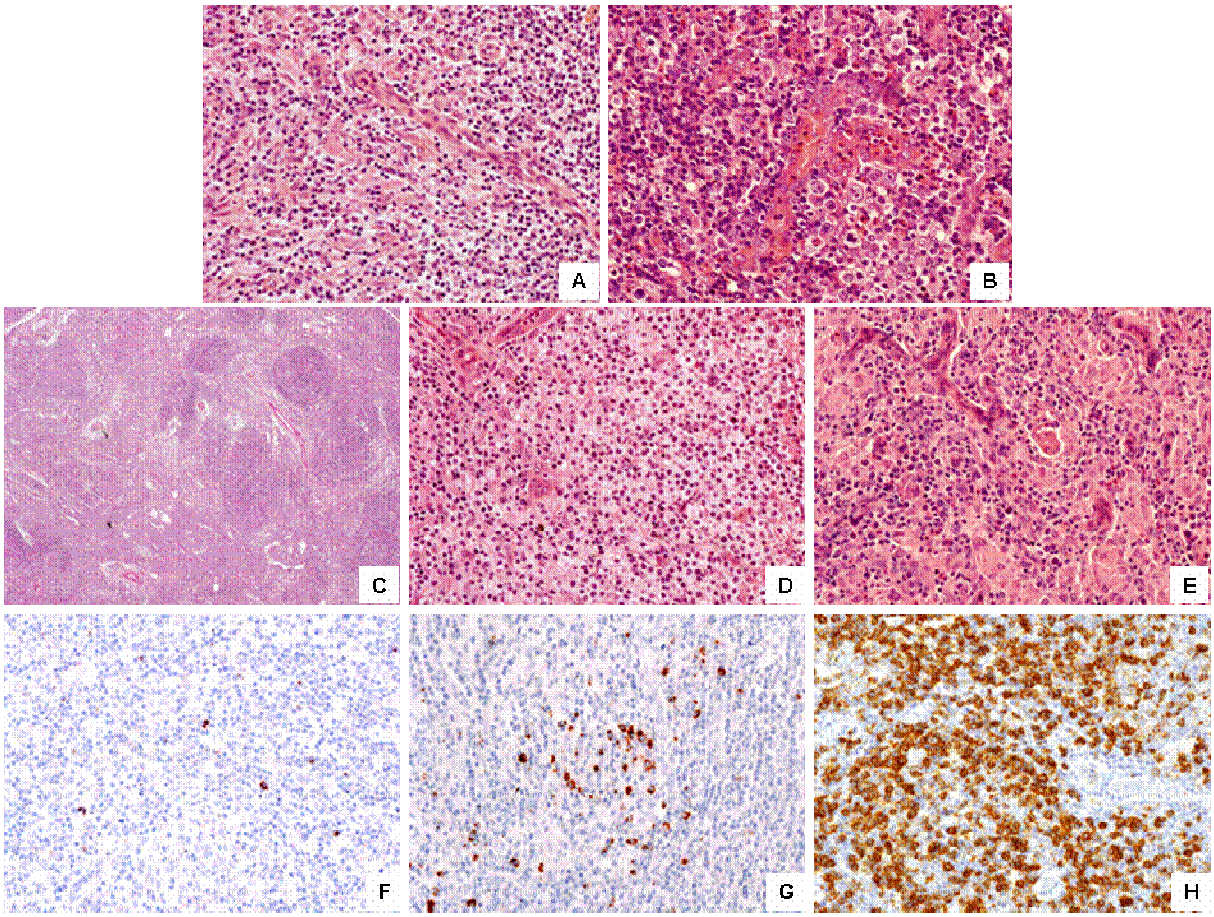

Figure 1

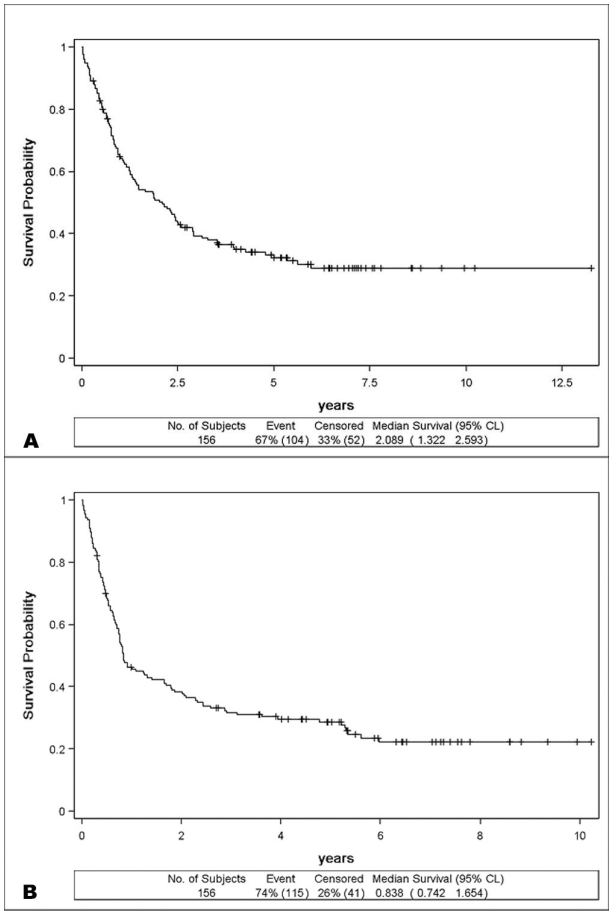

Figure 2

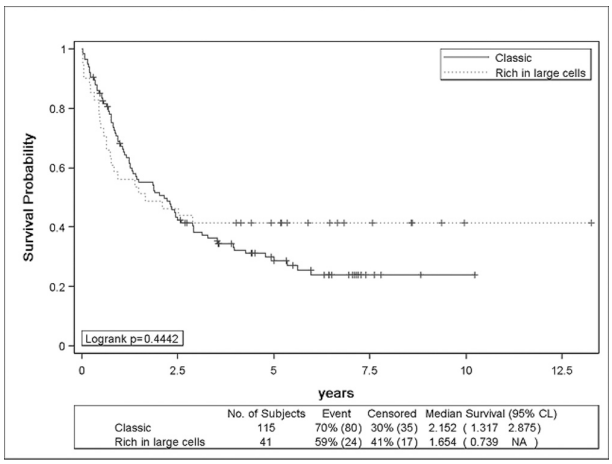

Figure 3

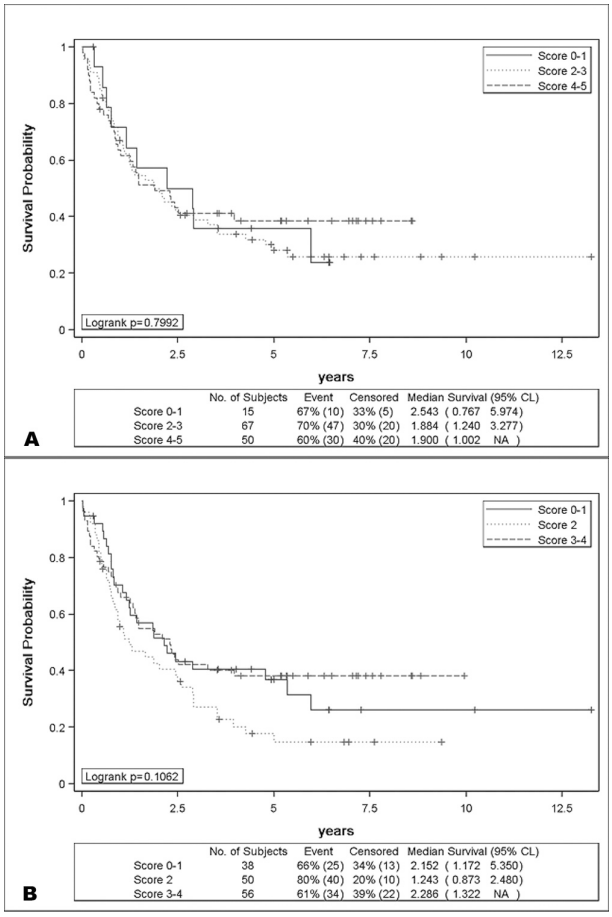

Figure 4