Composite lymphomas – *diagnosis and evolution*

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GROUNDS FOR SELECTING THESE PATIENTS

The composite lymphomas are defined as two different subtypes of clone proliferation, unrelated neither morphologically nor genetically, but which occur in the same anatomical region. First, the diagnosis was performed using merely morphological criteria, but starting with the use of molecular biology and immunological – histological chemistry techniques it became obvious that many of the so-called "composite lymphomas" no longer meet the criteria required for being classified as such (1).

Due to the fact that the diagnosis of such rarely encountered lympho-proliferative entities has recently increased and to the huge progresses in molecular biology and immunological histological chemistry, monitoring and treating such pathology has became quite a challenge. We selected two cases of composite lymphomas hospitalized in our clinic in 2005, and we further describe the case particularities with focus to their diagnosis, evolution and therapeutic options. ❑

CASE REPORT 1

Female, P.M., 51 – years old

Hereditary and Collateral History: irrelevant;
Personal Pathological History:

- Gigantic uterine fibroma, for which a complete hysterectomy with bilateral annexectomy was performed in 1996;
- Lambliasis affecting the bile, duodenum and intestine;
- Biliary dyskinesia;
- Chronic gastroduodenitis;
- Spastic colitis;
- Chronic tonsillitis;
- Neurotic syndrome;

Medical History

The patient first presented to our clinic in *July 2004* having a right lateral cervical adenopathy; a lymph node biopsy was performed, and the histological pathology and immune-chemistry tests reveal:

1. Pathologic histology*: modified lymph node with pseudo-nodular lymphoid proliferation with small cells, and relatively frequent Sternberg-Reed giant cells;*
2. Immune histological chemistry tests*:*
   - *CD20 positive, cytoplasmic, in frequent tumor cells;*

- *CD15 positive, granular, paranuclear;*
- *CD30 positive, granular, paranuclear, in frequent tumor cells;*
- *Bcl2 positive in tumor cells;*
- *CD21 positive in very frequent dendrite cells in the nodular regions.*

THE CONCLUSION WAS:

Composite lymphomas: Hodgkin lymphoma of a classical type, unclassifiable, associated with a malignant non-Hodgkin lymphoma with follicular small B-cells type I – centrocyte

No treatment was performed until March 2005 when the patient presented to our clinic having:

- Generalized poly-adenopathy above and below the diaphragm, sized 1 to 3 centimeters, the lymph nodes being confluent and building up adenopathy blocks, mobile with regard to the neighboring structures, with a firm consistency and completely painless;
- General unspecific signs of disease (weight loss over 8 kg during the past two months, feverish – more than 38'C, diffuse transpiration);
- No hepatosplenomegaly signs were depicted.

Laboratory and imagistic findings

- Slight anemia (10g/dl); leucocytes within the normal range values, without any malignant lymphocyte peripheral discharge; platelets within the normal range values;
- An important inflammation biological syndrome (VSH over 150mm/h; fibrinogen 800mg/dl; positive C-reactive protein);
- Normal range of LDH;
- Renal and hepatic functions within the normal range parameters;
- Medullar biopsy: enriched bone marrow, especially with regard to the granulocytic and megakaryocytic series, with shape abnormalities in most of the cellular series. No lymphoma determination was depicted at the medullar level;
- Chest x-ray: no secondary pathological determinations;
- Abdominal ultrasound: increased lymph nodes below the diaphragm, retroperitoneal, between the aorta and vena cava and inside the hepatic hilum, with no secondary determinations within the intra-abdominal parenchymal organs; without any hepatosplenomegaly signs.

Positive diagnosis

Composite lymphoma: classical unclassifiable Hodgkin lymphoma, associated with a malignant non-Hodgkin diffuse lymphoma with B-type small follicular cells, type – centrocyte; stage IIIB

Treatment

The patient underwent to 6 poly-chemo-therapy CHOP cures (Cyclophosphamide, Adriablastine, Vincristine, Prednisone); the outcome of the patient was favorable so far – a remission of the tumor syndrome without complete disappearance of the adenopathy and a complete regression of the inflammatory biological syndrome, without any significant complications related to the disease or to the administration of chemotherapy. ❑

CASE REPORT 2

Male, C.C.G., 37 – years old

Hereditary/Collateral and Personal Pathological History: irrelevant

Medical History

The patient first reported to the physician in *June 2004* presenting left inguinal adenopathy; the increased lymph nodes were extirpated and the pathological histology and immune chemistry reports revealed:

1. Pathological histology report*: modified lymph node, with two distinct types of regions: regions characterized by a nodular pattern, containing epithelial and rare tumor cells, located at the center of the region, resembling "popcorn", and low-cell-count regions, characterized by an important sclerosis, with frequent single- or double-nuclei tumor cells*.

2. Immune chemistry report*:*
   - *CD20 positive, cytoplasmic, in frequent tumor cells; positive in relatively frequent small lymphocytes in the nodular regions; positive in isolated small lymphocytes in the sclerosis regions;*
   - CD15 positive in granulocytes, negative in tumor cells;
   - *CD30 positive in plasmocytes, negative in tumor cells;*

- *EMA positive in isolated tumor cells;*
- *UCHL1 positive in very frequent small lymphocytes;*
- *Bcl2 positive in isolated tumor cells, positive in frequent small lymphocytes;*
- *Lambda positive in frequent tumor cells;*
- *CD23 positive only in rare dendrite cells in the nodular regions;*
- *NK1 positive in very frequent cells in the nodular regions – surrounding the tumor cells and dispersed in the sclerotic regions;*

THE CONCLUSION WAS:

Composite lymphoma: Hodgkin lymphoma – lymphocyte predominance, nodular type (Poppema lymphoma) associated with a malignant non-Hodgkin diffuse lymphoma with large B cells, rich in reactive T lymphocytes)

The patient did not receive any additional treatment until April 2005, when the left inguinal increased lymph node recidivated; a new biopsy confirms a recidivated composite lymphoma of the same type. Local examination showed left inguinal adenopathy block sized 7/10 centimeters, painless, of a kidney-like consistence without an adherence to the nearby structures. There were not any general signs of disease.

Laboratory findings

The complete blood count was within the normal ranges, a slight inflammatory syndrome was noted, LDH was slightly increased;

The hepatic and renal functions were within the normal range intervals;

Medullar biopsy showed normal hematopoietic function in all cell series, without any signs of lymphoma infiltration;

The CT revealed no other determinations than the left inguinal tumor lymph node group;

Positive diagnosis

Composite lymphoma: Hodgkin lymphoma – lymphocyte predominance, nodular type associated with a malignant diffuse non-Hodgkin lymphoma with large B-cells, rich in reactive T lymphocytes, stage IIA

Treatment

The patient underwent to 6 cures of CHOP poly-chemotherapy, and subsequently had a favorable evolution – a complete remission until the present, a complete reduction of the tumor block and the regression of the biological inflammatory syndrome, without any significant complications regarding the disease or to the chemotherapy so far. ❑

COMMENTS AND CONCLUSIONS

We rarely encounter composite lymphomas in our daily medical practice. The frequency amongst the non-Hodgkin lymphomas has increased, partly due to the progresses of the diagnoses techniques (a full pathological histology examination plus the immune chemistry and molecular biology techniques). Based on the two selected cases previously reported we noted that their evolution was relatively benignant despite of the lack of treatment (based on personal reasons – the patients temporarily refused any form of medical treatment): the tumor syndrome underwent to a slow, progressive evolution and associated general signs of disease and a biochemical expression (increased LDH, biologic inflammatory syndrome). Subsequent to the initiation of the treatment the disease has proven to be chemo-sensitive and a hematological response was noted (partial/apparently complete remission). It was maybe due to the rarity of the disease and to the fact that we never identified in the literature any specific predictive indexes of the composite lymphoma outcome, since the literature data mostly overlapped with the indexes cited for the Non-Hodgkin lymphomas or for the Hodgkin disease.

We further intend to conduct a viral serological screening for the EBV and some other gamma-herpes-viruses involved in the etiological pathogenesis of the malignant lymph proliferation, as well as some cytogenic and molecular biological tests. ❑

BRIEF REVIEW OF THE ETIOLOGICAL PATHOGENESIS OF THE COMPOSITE LYMPHOMAS

The lymphomas actually represent clonal malignant proliferations of the T, B or more rarely of the Natural Killer lymphocytes. Several different types of lymph proliferations occurring in the same patient were first described in 1954, based on morphologic pathology reports. The

term of composite lymphomas was first used in the Working Formulation classification for defining those distinct lymphomas in which two different subtypes of Malignant Non-Hodgkin lymphomas coexist, or in which the Hodgkin disease is associated with a malignant Non-Hodgkin lymphoma in the same patient, and proliferate within the same organ or tissue. Using the new immune chemistry tests and molecular biology techniques it was demonstrated that the two different morphologic subtypes do not necessarily represent two different types of lymph proliferation with a distinctive clonal origin. In many of these cases the so-called composite lymphoma may actually result from a clonal modification and further development respecting two different pathways of the same common precursor, which argues with the original definition of the disease (1).

Considering the subtypes of cell populations proliferating, the composite lymphomas may be divided into:

- Two subtypes of B-cell-type non-Hodgkin lymphomas;
- Two subtypes of T-cell-type non-Hodgkin lymphomas (very rare);
- One subtype of B-cell-type non-Hodgkin lymphoma mixed with a subtype of T-cell-type non-Hodgkin lymphoma;
- One subtype of B-cell-type non-Hodgkin lymphoma mixed with a subtype of the Hodgkin disease.

When studied using molecular analysis techniques (amplification of the rearranged genomic regions of the heavy chain of the IgM immunoglobulin), several cases of true bi-cloning were reported (thus, different clonal re-arrangements were obtained, suggesting that two precursor cells were at the origins of the proliferative process), as well as some cases when the same common clonal precursor was reported (suggesting that there was a common progenitor cell for both proliferative lines) (2). In the context of the original definition, the composite lymphomas represent tumors with proliferative components which present with different morphologic and immune phenotype characteristics, which do not originate in the same common precursor. In order to certainly classify such cases as subtypes of composite lymphomas, an important role is played by studying the variable V regions in the immunoglobulin chain, which are characterized by a wide diversity and specificity as part of the B-line, and which during the T-lymphocyte-dependent immune response (restricted to the germinal center) represents the main localization of a somatic hyper-mutation process informative of the differentiation stage of the respective B-lymphocyte (3). The configuration of the light-chain genes is consistent throughout the DNA structure, while significant differences are noted in the configuration of the variable regions of the heavy chains. Further analysis of the heavy chain region genes seems to indicate that the differences between the various DNA configurations most likely occur due to post-rearrangement deletions occurring either on the constant region or on the variable region of the m chain. Hence the genetic instability of the DNA sequences within the, or surrounding the variable region of the m chain may result in a bi-clonal proliferation and further lead to the apparition of the two populations proliferating as part of the composite lymphomas.

After analyzing the amplification of immunoglobulin gene rearrangements, it was proven that the Sternberg-Reed cells in the composite lymphomas associating a proliferative component of the Hodgkin disease most frequently derive from the B-lymphocyte in the germinal center. It was generally proved that the Sternberg-Reed cell in the Hodgkin disease (the lymphocyte predominant subtype) derives from a B-lymphocyte selected by the antigen within the germinal center, while the Sternberg-Reed cells noted in other classical subtypes of the Hodgkin disease originate in the pre-apoptotic B lymphocyte located in the germinal center. The Sternberg-Reed cell rarely derives from the T lymphocyte. During its evolution the Sternberg-Reed loses its genetic programming expressed in the B cell line, which explains why the cell shows no B-line receptors and also suggests that at least one of the events involved in the pathogenicity of the Hodgkin disease influences the identity of the cell line.

It was also suggested that in the cases where there is an identifiable common precursor at a germinal center level there are some different mutational elements which make this common precursor evolve either towards the Sternberg-Reed cell or towards the malignant lymphocyte encountered in the non-Hodgkin lymphoma (3).

An important role was attributed to the EBV, quite frequently identified in the composite lymphomas, which might suggest the existence of a common precursor infected with the EBV. It was also noted that in composite lymphomas the EBV is usually present in the Sternberg-Reed cell, which seems to indicate that the virus might play a role in the development of the proliferative component of the Hodgkin disease as part of composite lymphomas. From general and morphologic points of view, the EBV-positive cases seem to lack some of the characteristic infiltration usually occurring in the Hodgkin disease (4).

The most frequently cited chromosome abnormalities are (6):

- Translocations, like bcl2/IgH or CCND1/IgH, which seem to represent early events in the pathogenicity of composite lymphomas;
- Restriction of the TP53 gene in both alleles, which might exemplify a late event most likely occurring within the germinal center and affecting the evolution of a common lymphocyte precursor.

The composite lymphomas are in fact, a category of lymphomas quite histologically discordant, which may occur either synchronously or sequentially in the same anatomical location without being clonally related. In this context, diagnoses of the composite lymphomas might be actually underestimated, since not all affected locations may undergo to biopsies and since the biopsies are performed according to clinical reasoning. A precise evaluation would mean a histological analysis of all locations involved in the diagnostic process and in the relapses. The richterian transformation, meaning the progression of the lymphoma from a low-malignity phase towards a high-malignity lymphoma, is not considered a composite lymphoma. However there are citations of known cases of malignant non-Hodgkin lymphomas which were initially identified as indolent, but the biopsy revealing composite lymphoma characteristics. At first it was believed that this is due to the progression of the disease from one stage to another, but the molecular analysis showed a different clonal origin of the proliferative components, which lead to classifying such situations as true composite lymphoma (7).

The suggested etiologic and pathogenic mechanisms include:

- Genetic instability;
- Spontaneous or treatment – induced differentiation;
- Deficits in immunological supervision;
- Oncogenic viral infections (8).

Considering the evolution, since the response to therapy does not differ too much from the other patients with malignant non-Hodgkin lymphomas, the long-term survival is significantly shorter, a worse prognosis being most-likely due to different pathogenic mechanisms.

The prognosis for such subtypes of lymphomas depends on the histological subtype of malignant non-Hodgkin lymphoma. The composite lymphoma in which the histological subtype of malignant non-Hodgkin lymphoma suggests intermediate or high malignity has a reserved prognostic, given by the aggressive model of malignant non-Hodgkin lymphoma; in case of a histological subtype of malignant non-Hodgkin lymphoma suggestive of reduced malignity, the overall prognosis depends on the Hodgkin component of the lymphoma. ❑

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