



EHA-GBMTA-AHA
Hematology Tutorial:
New aspects in diagnostic
choices and treatment
options of hematological
malignancies

Self-assessment case
Hodgkin Lymphoma

Igor Aurer

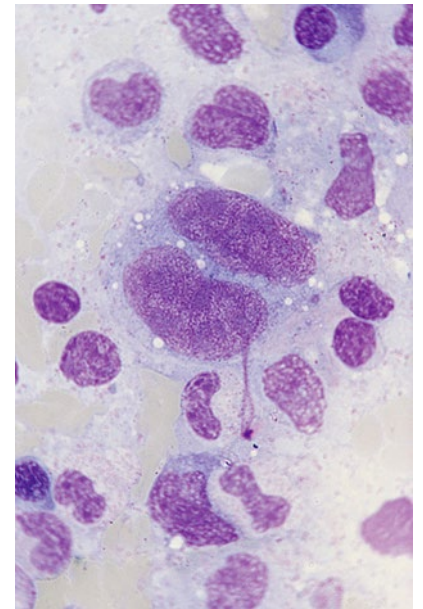
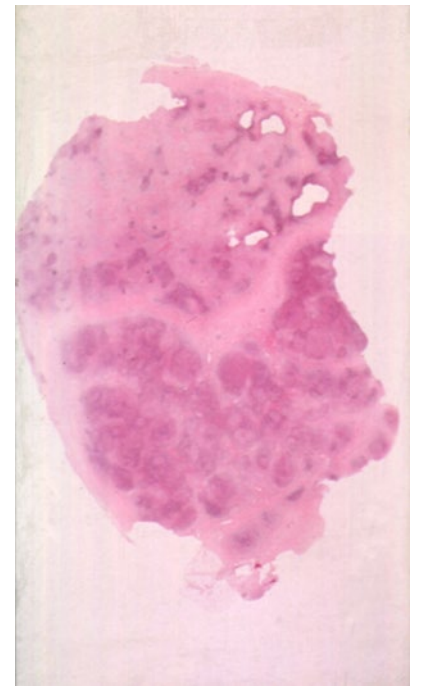


Clinical history

A 26-year-old woman with a 2 months history of night sweats and itching was referred to a hematologist with cervical lymphadenopathy.

Lymph node biopsy was consistent with Hodgkin's lymphoma, nodular sclerosis type 1.

PET-CT showed bulky mediastinal (13x8 cm) and left cervical FDG-avid lymphadenopathy (3x2 cm).



Q1) Which of the following statements is true?

1. A bone marrow biopsy is needed to stage this patient.
2. Erythrocyte sedimentation rate (ESR) is needed to determine into which prognostic group this patients belongs.
3. This patient should be treated as having localised disease.
4. This patients should be treated as having advanced-stage disease.
5. There is no expert consensus as to whether this pattern of disease should be treated as localised or advanced.

Q1) Which of the following statements is true?

1. A bone marrow biopsy is needed to stage this patient.
2. Erythrocyte sedimentation rate (ESR) is needed to determine into which prognostic group this patients belongs.
3. This patient should be treated as having localised disease.
4. This patients should be treated as having advanced-stage disease.
5. There is no expert consensus as to whether this pattern of disease should be treated as localised or advanced.

Q1 - discussion

- Bone marrow biopsy is not considered necessary in newly diagnosed HL patients who have been staged with PET, because PET is more sensitive for detection of bone marrow disease.
- This patient has bulky mediastinal disease which puts her in the unfavorable prognostic group irrespective of ESR.
- Patients with B symptoms and bulky mediastinal involvement are considered advanced-stage disease according to the German Hodgkin Study Group (GHSG), but not European Organisation for Research and Treatment of Cancer (EORTC) and Groupe d'Etude des Lymphomes de l'Adulte (LySA).

Clinical history

The patient received 1 cycle of ABVD.

Treatment was followed by significant nausea and vomiting.

B symptoms disappeared and the cervical lymph nodes regressed.

The patient refused further treatment.

Q2) Which of the following statements is true?

1. Interrupting treatment is undesirable and may significantly worsen prognosis.
2. The progression-free survival (PFS) of patients treated with ABVD and eBEACOPP in this setting is similar.
3. AVD+brentuximab vedotin (Bv) is approved for treatment of stage II Hodgkin's lymphoma.
4. ABVD and AVD+Bv have similar hematologic toxicity.
5. eBEACOPP is more emetogenic than ABVD.

Q2) Which of the following statements is true?

1. Interrupting treatment is undesirable and may significantly worsen prognosis.
2. The progression-free survival (PFS) of patients treated with ABVD and eBEACOPP in this setting is similar.
3. AVD+brentuximab vedotin (Bv) is approved for treatment of stage II Hodgkin's lymphoma.
4. ABVD and AVD+Bv have similar hematologic toxicity.
5. eBEACOPP is more emetogenic than ABVD.

Q2 - discussion

- PFS of patients with localised-stage unfavorable or advanced-stage Hodgkin's lymphoma treated with eBEACOPP is significantly better than if they're treated with ABVD.
- AVD+ brentuximab vedotin (Bv) is approved for front-line treatment of stage III and IV cHL.
- AVD+Bv has more haematologic toxicity than ABVD and should (as eBEACOPP) be administered with G-CSF prophylaxis.
- Dacarbazine is the most emetogenic drug in these regimens. Intensive anti-emetic prophylaxis is indicated with ABVD, AVD+Bv and BrECADD.
- It is the general experience of physicians treating HL that interrupting therapy results in an outgrowth of resistant neoplastic clones, significantly reducing the chance of favorable outcomes.

Clinical history

Six months later she presented with bilaterally enlarged cervical lymph nodes, predominantly on the left side, with night sweats and weight loss

Laboratory results:

ESR- 52mm/hr, Hb- 111 g/L, WBC- $14.2 \times 10^9/L$,
Lymphs- $6.0 \times 10^9/L$, albumin- 33.4 g/L

PET-CT

Mediastinal lymph node conglomerate 19x11 cm, bilateral cervical lymph nodes 5x3 cm, bilateral axillary lymph nodes 2x1.3 cm, left pleural effusion 7-8 cm



Treatment

- **Six courses of eBEACOPP**
- *Treatment complications:*
 - 2 episodes of febrile neutropenia
 - 1 dose reduction because of thrombocytopenia
 - No need for treatment delay
- **PET-CT:** 3 weeks after the end of treatment
 - Mediastinal lymph node conglomerate 14x7 cm, Deauville 4
 - Left cervical lymph node 2x1 cm, Deauville 3, axillary lymph node 1x1 cm, Deauville 2
- **Radiotherapy 30 Gy to involved mediastinal nodes was administered**

Q3) Which of the following statements is **incorrect**?

1. Controlled studies have shown interim PET to be useful for **escalating** therapy in patients initially treated with **ABVD**.
2. Controlled studies have shown interim PET to be useful for **escalating** therapy in patients initially treated with **AVD+Bv**.
3. Controlled studies have shown interim PET to be useful for **de-escalating** therapy in patients initially treated with **eBEACOPP**.
4. Radiotherapy to sites of localised PET+ disease can convert PR into CR.
5. When evaluating PET results, Deauville 3 is considered negative and 4 positive.

Q3) Which of the following statements is **incorrect**?

1. Controlled studies have shown interim PET to be useful for **escalating** therapy in patients initially treated with **ABVD**.
2. Controlled studies have shown interim PET to be useful for **escalating** therapy in patients initially treated with **AVD+Bv**.
3. Controlled studies have shown interim PET to be useful for **de-escalating** therapy in patients initially treated with **eBEACOPP**.
4. Radiotherapy to sites of localised PET+ disease can convert PR into CR.
5. When evaluating PET results, Deauville 3 is considered negative and 4 positive.

Relapse

- Two months later the patient presented at an unscheduled visit because of a palpable node in the right axilla
Core needle biopsy – **Diagnosis: classical HL**
- **PET-CT:** left supraclavicular lymph node 3x1.8 cm, mediastinal mass 15x8 cm (PET-neg), right axillary lymphadenopathy 3x2.8 cm, supra-diaphragmatic lymph nodes 3.5x2.3 cm
- Metabolic and morphological progression
- **Bone marrow biopsy:** no tumor infiltration
- No B symptoms
- ESR- 21, Hb- 116 g/L
- **Refractory Hodgkin lymphoma**



Q4) How would you treat this patient now?

1. With a different standard-dose chemotherapy regimen (e.g. C-MOPP) followed by involved node radiotherapy.
2. With Bv monotherapy.
3. With a PD-1 inhibitors (PD-1i), e.g. pembrolizumab or nivolumab, as monotherapy.
4. Using high-dose chemotherapy (with or without a newer agent) followed by autologous stem cell transplantation (ASCT) in case of PET-negative remission.
5. With high-dose chemotherapy (with or without a newer agent) followed by ASCT only if there is a PET-positive partial remission.

Q4) How would you treat this patient now?

1. With a different standard-dose chemotherapy regimen (e.g. C-MOPP) followed by involved node radiotherapy.
2. With Bv monotherapy.
3. With a PD-1 inhibitors (PD-1i), e.g. pembrolizumab or nivolumab, as monotherapy.
4. Using high-dose chemotherapy (with or without a newer agent) followed by autologous stem cell transplantation (ASCT) in case of PET-negative remission.
5. With high-dose chemotherapy (with or without a newer agent) followed by ASCT only if there is a PET-positive partial remission.

Third line treatment

The patient received 2 cycles of DHAP+Bv

Treatment complications:

1x febrile neutropenia, required hospitalization

Grade IV anemia, thrombocytopenia and neutropenia

Grade III mucositis

PET-CT: no signs of metabolically active disease

Stem cells were collected after the 3rd cycle

Patient underwent ASCT after BeEAM conditioning

Gram positive sepsis

Diarrhoea

Hematological recovery on day +14

Bv monotherapy was continued for a total of 16 cycles



Q5) Which of the statements below is correct?

1. Randomised studies showed that the addition of Bv or a PD-1i to high-dose chemotherapy increases overall survival (OS).
2. Phase II studies suggest that the addition of Bv or a PD-1i to high-dose chemotherapy increases response rates and PFS.
3. Bv-containing combinations have been shown to be superior to PD-1i-containing combinations.
4. Bv maintenance after ASCT in high-risk patients should continue until progression or unacceptable toxicity.
5. Regarding Bv maintenance, needing more than 2 lines of therapy to achieve remission does not qualify as high risk.

Q5) Which of the statements below is correct?

1. Randomised studies have shown that the addition of Bv or a PD-1i to high-dose chemotherapy increases overall survival (OS).
2. Phase II studies suggest that the addition of Bv or a PD-1i to high-dose chemotherapy increases response rates and PFS.
3. Bv-containing combinations have been shown to be superior to PD-1i-containing combinations.
4. Bv maintenance after ASCT in high-risk patients should continue until progression or unacceptable toxicity.
5. Regarding Bv maintenance, needing more than 2 lines of therapy to achieve remission does not qualify as high risk.

Q5 - discussion

1. **No randomised studies** of high-dose chemotherapy ± newer agents in R/R HL have been performed.
2. Phase II studies consistently show that the combinations result in **superior response rates and PFS**, but there is no clear-cut advantage of either of the newer agents over the other.
3. As per study, Bv maintenance should be given for **up to 16 cycles**.
4. Risk factors fulfilling requirements for Bv maintenance after ASCT are:
 - primary refractory disease or early relapse
 - extranodal disease or B symptoms at relapse
 - need for more than 2 lines to achieve CR
 - **not achieving CR prior to ASCT**

Q6) Which of the following statements regarding follow-up is incorrect?

1. This patient is at increased risk of developing heart disease and should be educated about appropriate life-style adjustments.
2. This patient is at an increased risk of developing secondary malignancies and should start with breast cancer screening early.
3. This patient needs regular imaging during follow-up.
4. Methods to reduce infertility risk in female HL patients include use of GnRH analogues, oocyte and ovarian tissue cryopreservation.
5. PD-1i and allogeneic stem cell transplantation have been shown to be effective in HL patients relapsing after ASCT and Bv maintenance.

Q6) Which of the following statements regarding follow-up is incorrect?

1. This patient is at increased risk of developing heart disease and should be educated about appropriate life-style adjustments.
2. This patient is at an increased risk of developing secondary malignancies and should start with breast cancer screening early.
3. This patient needs regular imaging during follow-up.
4. Methods to reduce infertility risk in female HL patients include use of GnRH analogues, oocyte and ovarian tissue cryopreservation.
5. PD-1i and allogeneic stem cell transplantation have been shown to be effective in HL patients relapsing after ASCT and Bv maintenance.

Q6 - discussion

- Patients treated for HL are at increased risk of infertility, secondary malignancies and cardiac disease.
- Methods to reduce the risk of infertility, if needed, should be implemented before or at time of start of antineoplastic therapy.
- Patients should be warned about cardiac risk factors and educated on their reduction.
- In females, breast cancer detection programs should be started early.
- Routine imaging does not improve outcome of relapsing lymphoma and should be avoided.
- Both PD-1i and alloSCT (in responding patients) are useful in patients failing high dose chemotherapy, ASCT and Bv.

Clinical history

- The patient is in continuous remission and well >6 years after ASCT.
- She attends regular breast cancer screening examinations.
- She performs regular physical exercise, watches her weight and does not smoke.
- The patient refused GnRH analogue therapy at start of treatment.
 - Not interested in progeny.
- HL is a rare malignancy with 2, 3 or even 4 chances for cure!



EHA-GBMTA-AHA
Hematology Tutorial:
*New aspects in diagnostic
choices and treatment
options of hematological
malignancies*

Self-assessment case:
*Hodgkin Lymphoma in an
elderly person with HIV*

Igor Aurer



Clinical history - 1

A 61-year-old man with a 2 months history of night sweats, weight loss and dry cough was referred by his infectologist to a hematologist for cervical lymphadenopathy.

HIV infection for 21 years, PCR negative, CD4+ count 150/ μ l, currently receiving biktgravir, emtricitabine and tenofovir.

History of past tuberculosis, syphilis, myositis.

Lymph node biopsy was proposed, but patient went **instead** to **consult** with his guru in India.

Q1) Which of the statements regarding lymphomas in patients living with HIV is true?

1. Lymphomas are NOT a major cause of death in this population.
2. The incidence of lymphomas is similar to that of the age- and gender-matched general population.
3. The incidence of aggressive NHL has remained stable despite the introduction of HAART.
4. The incidence of HL has increased slightly and then remained stable after the introduction of HAART.
5. The incidence of both, NHL and HL, is increased in patients with very low (<100) CD4 counts

Q1) Which of the statements regarding lymphomas in persons living with HIV is true?

1. Lymphomas are NOT a major cause of death in this population.
2. The incidence of lymphomas is similar to that of the age- and gender-matched general population.
3. The incidence of aggressive NHL has remained stable despite the introduction of HAART.
4. The incidence of HL has increased slightly and then remained stable after the introduction of HAART.
5. The incidence of both, NHL and HL, is increased in patients with very low (<100) CD4 counts

Q1 - discussion

Lymphomas are the most common type of cancer and a leading cause of mortality in people who are living with HIV.

The incidence of NHL was markedly reduced after the introduction of ART in the mid-1990s, while the incidence of HL increased slightly and then remained stable since 2000.

The incidence of NHL is increased in patients with very low, and HL in those with moderately decreased CD4 counts.

Compared with the age- and gender-matched general population, the incidences of NHL and HL are 10- to 20-fold higher.

The most common histological types of HIV-associated lymphomas are DLBCL (37%), HL (26%) and BL (20%).

Clinical history - 2

Three months later the patient returned from India due to **worsening general condition**, continuous **fever, weight loss** (20 kg in 2 months) and further **enlargement of cervical lymph nodes**. A urinary catheter had to be inserted because of **urine retention**. Medications included HAART and antibiotics for presumed pneumonia and proven urinary tract infection (Enterococcus).

ECOG **PS 2, fever >38°C**, 178 cm, 68 kg, bilateral cervical lymphadenopathy up to 5 cm, lungs clear, systolic murmur 3/6 on the aortic valve, liver palpable for 2 cm, spleen not palpable, left scrotal hernia, no pitting edema, **walks with short insecure steps worsening with eye closure**.

WBC $18.2 \times 10^9/l$, Hb 86 g/l, MCV 89 fl, T 49, ANC 15.8, **lymphocytes** 6%, direct antiglobulin test +

Cervical lymph node core-needle and bone marrow biopsy, body CT scan, brain MRI and LP were performed.

Diagnostic findings

Lymph node biopsy: effaced with hyalinized connective tissue bundles surrounded by numerous small and medium sized T lymphocytes, some of which are atypical and mostly of the T-helper phenotype (CD3+, CD4+, PD1-, BCL6-), plasma cells and eosinophils as well as single large multinuclear and mononuclear cells with prominent large eosinophilic nucleoli, corresponding to Hodgkin and Reed-Sternberg cell variants. The described large atypical cells are CD20-, PAX5+, CD30+, CD15+, CD3-, EBER+. TCR is polyclonal. These findings are consistent with the diagnosis of **classical Hodgkin lymphoma (cHL)**.

Bone marrow biopsy: No signs of lymphoma infiltration.

CT: Enlarged cervical lymph nodes, up to 4.5 cm. Bulky mediastinal lymphadenopathy. Liver normal, spleen enlarged to 15 cm with multiple hypovascular lesions up to 8 cm. Renal cysts. Retroperitoneal lymph nodes up to 3 cm forming conglomerates. Left sided inguinal hernia. Focal mass in Th XI.

Brain MRI: small non-specific hyperintensive lesions consistent with vascular lesions. Mild cerebral atrophy.

Heart US: LVEF 70%, no hemodynamically significant valvular disorder

LP: normal

Q2) What about our patient?

1. Brain involvement is frequent in HIV+ HL and PTCL patients. The MRI is probably misinterpreted.
2. Clinical presentation and distribution of histological cHL subtypes does not differ between HIV+ and HIV- HL patients.
3. The CT findings explain the patient's neurological symptoms. A neurologic consultation is not needed.
4. Steroids should not be administered because of increased risk of infectious complications.
5. The probability that the patient has PTCL and not cHL is exceedingly low.

Q2) What about our patient?

1. Brain involvement is frequent in HIV+ HL and PTCL patients. The MRI is probably misinterpreted.
2. Clinical presentation and distribution of histological cHL subtypes does not differ between HIV+ and HIV- HL patients.
3. The CT findings explain the patient's neurological symptoms. A neurologic consultation is not needed.
4. Steroids should not be administered because of increased risk of infectious complications.
5. The probability that the patient has PTCL and not cHL is exceedingly low.

Q2 - discussion

Patients with HIV and HL usually present with advanced stage disease. Mixed cellularity subtype is more frequent than nodular sclerosis. The lymphocyte depleted subtype is significantly more frequent than in HIV-patients. B symptoms are frequent, but brain involvement remains extremely rare.

In patients with large tumor mass or severe symptoms, steroids are useful for reducing symptoms, improving patient condition and reducing the toxicity of the first chemotherapy cycle.

PTCL is infrequent in HIV+ patients and polyclonal TCR effectively rules out this diagnosis.

Q3) Which of the statements regarding therapy of HL in persons living with HIV is true?

1. Patients younger than 60 years do not tolerate ABVD.
2. Indications for autologous stem cell transplantation (ASCT) are the same as in HIV- cHL patients.
3. Patients tolerate escalated BEACOPP as good as age-matched HIV-patients.
4. Radiotherapy should be avoided because of a very high incidence of secondary tumors.
5. PD-1 inhibitors are not useful because of the immunosuppression inherent to HIV.

Q3) Which of the statements regarding therapy of HL in persons living with HIV is true?

1. Patients younger than 60 years do not tolerate ABVD.
2. Indications for autologous stem cell transplantation (ASCT) are the same as in HIV- cHL patients.
3. Patients tolerate escalated BEACOPP as good as age-matched HIV-patients.
4. Radiotherapy should be avoided because of a very high incidence of secondary tumors.
5. PD-1 inhibitors are not useful because of the immunosuppression inherent to HIV.

Q3 - discussion

Patients with HIV and HL tolerate ABVD and radiotherapy similar as HIV-.

The risk of infectious complications of escalated BEACOPP is, however, increased.

Indications for ASCT are the same as in HIV- patients.

PD-1 inhibitors have been shown to be effective.

Hübel K et al, "HIV-associated lymphomas: EHA-ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2024 "

Q4) Which of the statements regarding therapy of HL in elderly persons is true?

1. Escalated BEACOPP has been shown to be feasible and effective in fit patients older than 60.
2. BrECADD has been shown to be feasible and effective in fit patients older than 60.
3. AVD+brentuximab vedotin (AVD+Bv), concomitant or sequential, has been shown to be feasible and effective in fit patients older than 60.
4. AVD + nivolumab has NOT been shown to be feasible and effective in fit patients older than 60.
5. Pulmonary toxicity of ABVD does NOT increase with age.

Q4) Which of the statements regarding therapy of HL in elderly persons is true?

1. Escalated BEACOPP has been shown to be feasible and effective in fit patients older than 60.
2. BrECADD has been shown to be feasible and effective in fit patients older than 60.
3. AVD+brentuximab vedotin (AVD+Bv), concomitant or sequential, has been shown to be feasible and effective in fit patients older than 60.
4. AVD + nivolumab has NOT been shown to be feasible and effective in fit patients older than 60.
5. Pulmonary toxicity of ABVD does NOT increase with age.

Q4 - discussion

- Escalated BEACOPP has been shown to be too toxic for patients older than 60, while the results of BrECADD in patients older than 60 have not been published so far.
- AVD+Bv has been shown to be reasonably safe and effective in fit patients older than 60, provided primary prophylaxis with G-CSF is used.
- Patients older than 60 have been included in the studies of AVD+nivolumab and did not have an increased incidence of side-effects.
- Pulmonary toxicity of bleomycin increases significantly with age; patients older than 65-70 years should not receive more than 2 cycles of ABVD.

Treatment - 1

The patient started on AVD+Bv.

Peg-filgrastim was administered to reduce the risk of neutropenic complications.

Steroids were continued because of AIHA and ITP.

B12 substitution was started because of low-normal B12 concentrations.

Patient had multiple infectious complications, necessitating antimicrobial treatment and leading to occasional treatment delays.

An attempt to stop catheterization was unsuccessful because of persistent urinary retention. He fell multiple times and remained bedridden because of left hip pain.

The neurologist asked for a spine MRI which showed possible infiltration of the sacral plexus by lymphoma.

Q5) Which of the statements is true?

1. Conventional filgrastim is as effective as pegylated filgrastim for prevention of complications of neutropenia.
2. When given prophylactically, filgrastim should be started only after WBC decreases.
3. Patients with neutrophil counts $>50 \times 10^9/l$ after administration of pegylated filgrastim are at risk of bone marrow exhaustion.
4. The risk of brentuximab vedotin induced neuropathy is NOT increased in HIV+ cHL patients.
5. In patients developing neuropathy the dose of brentuximab vedotin should be reduced.

Q5) Which of the statements is true?

1. Conventional filgrastim is as effective as pegylated filgrastim for prevention of complications of neutropenia.
2. When given prophylactically, filgrastim should be started only after WBC decreases.
3. Patients with neutrophil counts $>50 \times 10^9/l$ after administration of pegylated filgrastim are at risk of bone marrow exhaustion.
4. The risk of brentuximab vedotin induced neuropathy is NOT increased in HIV+ cHL patients.
5. In patients developing neuropathy the dose of brentuximab vedotin should be reduced.

Q5 - discussion

Pegilated filgrastim has been shown to be more effective than conventional for prevention of neutropenic fever. There is no danger of bone marrow exhaustion despite occasional hyperleukocytic reactions.

To achieve optimal efficacy G-CSF (conventional and pegilated) needs to be administered before neutropenia occurs.

Risk of Bv-related neuropathy is higher in patients with HIV.

In patients with neuropathy gr. 2 the dose of Bv should be reduced and in those without improvement or occurrence of gr. 3 and 4, stopped.

Treatment course - 2

- The dose of brentuximab vedotin was reduced after cycle 2 and withheld after cycle 4 because of neuropathy.
- Cotrimoxazole and acyclovir were administered continuously for prophylaxis of PIP and HSV/VZV reactivation.
- A CT scan performed after 3 cycles showed a decrease in lymph node size >50% and a 23 mm large left-side pubic and ischiadic osteolysis.
- The sacral plexus and osteolysis were irradiated. Left hip pain was substantially reduced, but patient remained bedridden. Urinary retention persisted.
- Laboratory findings improved.
- A PET-CT scan was performed after 6 cycles showing mediastinal lymph nodes up to 3.6 cm with a Deauville score 2, and a normal sized spleen with a Deauville score 3.

Q6) Which statement regarding the response of this patient is true?

1. He is in partial remission because the mediastinal lymph nodes are still enlarged.
2. He is in partial remission because of Deauville score 3 of the spleen.
3. He is in complete remission.
4. He has stable disease.
5. It is impossible to evaluate the response without performing a MRI.

Q6) Which statement regarding the response of this patient is true?

1. He is in partial remission because the mediastinal lymph nodes are still enlarged.
2. He is in partial remission because of Deauville score 3 of the spleen.
3. He is in complete remission.
4. He has stable disease.
5. It is impossible to evaluate the response without performing a MRI.

Conclusions

- After a difficult course, complete remission was achieved, but the patient remained dependent on personal assistance, mobile only with a walker and the aid of a physiotherapist.
- Steroids were successfully tapered.
- Folic acid, B12 supplementation and HAART were continued and the patient was transferred to a recovery facility for intensive physical therapy.
- An attempt to decatheterize the urinary bladder is scheduled within 2 months.