Прилози, Одд. биол. мед. науки, МАНУ, XXXII, 1, с. 313–321 (2011)
Contributions, Sec. Biol. Med. Sci., MASA, XXXII, 1, p. 313–321 (2011)
ISSN 0351–3254
УДК: 616.419-097

CASE REPORT

IMMUNOSUPRESSIVE TREATMENT WITH CYCLOSPORIN-A FOR A PATIENT WITH HYPOPLASTIC MYELODISPLASTIC SYNDROME: A CASE REPORT

Pavkovic M[1], Jovanovic R[2], Petrusevska G[2], Cevreska L[1], Stojanovic A[1]

[1]*University Haematology Clinic, Medical Faculty, Skopje, R. Macedonia*
[2]*Institute of Pathology, Medical Faculty, Skopje, R. Macedonia*

A b s t r a c t: *Backgraound:* Imunosupressive therapy with antithymocyte globulin (ATG), cyclosporine (CsA) or both has been shown to induce haematological responses in a subset of patients with myelodysplastic syndromes (MDS), in particular in the hypocellular form of MDS.

Case report: We report our first case with hypocellular MDS treated with CsA. A 54-year-old female referred to our Department due to weakness and severe pancytopenia. Hypocellular form of MDS was diagnosed after bone marrow biopsy. Treatment with CsA was started one year after diagnosis. Treatment with CsA resulted in clinical improvement, a very good partial haematological response, resolution of transfusion requirement and an increase in bone marrow cellularity.

Conclusions: In our experience, immunosuppressive treatment with CsA and/or ATG could be an alternative for patients with hypoplastic MDS for whom there is no possibility of allogenic bone marrow transplantation as only curative therapy.

Keywords: hypocellular myelodysplastic syndrome, pancytopenia, immunosuppressive therapy, cyclosporine A.

Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal haematopoietic stem cell disorders characterized by dysplasia in one or more of the haematopoietic cell lines, ineffective haematopoiesis resulting in peripheral

cytopenias and progressive evolution to acute leukaemia [1, 2]. Patients with MDS are older adults with comorbidities, and death from MDS is due to progression to acute leukaemia or to the consequences of cytopenia [3]. The International Prognostic Scoring System (IPSS) can predict survival based on clinical, haematological and karyotypic features [4]. The only curative treatment for MDS is allogenic bone marrow transplantation combined with aggressive chemotherapy [5], but due to the older age of the patients with MDS it is rarely a possible therapeutic approach. Most of the patients are treated with supportive care [6], haematopoietic growth factors [7], decitabine [8], lenalidomide [9], or immunosuppressive therapy with antithymocyte globulin and/or cyclosporine [10, 11] etc.

The bone marrow in patients with MDS is usually hypercellular or normocelluar with dysplastic characteristics. However, some investigators have reported MDS with hypocellular bone marrow with dysplastic hematopoesis as a separate clinicopathologic entity [12, 13]. It is characterized by severe thrombocytopenia, leucopenia and/or anaemia; karyotypic abnormalities are usually absent. Some authors consider hypoplastic MDS a subtype of aplastic anaemia (AA) [14]. Because hypoplastic MDS may be due to immune reaction against haematopoietic stem cells, and usually is not responsive to conventional therapy, there might be a role for immunosuppressive therapy (IST) such as antithymocyte globulin (ATG) or cyclosporine (CsA) in the treatment of this form of MDS [10, 11]. Immunosuppressive therapy has been shown to induce sustained haematological responses in a subset of patients with MDS. In this article, we report the first case of MDS treated with immunosuppressive therapy with CsA in our institution.

Case Report

A 54-year-old female, referred to our Department in May 2007 due to weakness and severe pancytopenia without any previous medical history. Her haemoglobin level was 68 g/L, leucocytes 2.6×10^9/L with absolute neutrophil count (ANC) 1.2×10^9/L, platelet count 49×10^9/L, MCV 101 fL and normal peripheral blood smear without blast or immature blood cells. The first bone marrow biopsy showed extremely hypocellular bone marrow with rare myeloid progenitors, pathohistological findings were severe hypoplastic anaemia and agranulocytosis. Because of pathohistological findings highly suspicious of aplastic anaemia, two weeks later we performed a contralateral iliac crest biopsy with similar pathohistological findings (extremely hypocellular bone marrow but with dysplastic characteristics of all three lineages, rare megakaryocytes and blast cells < 5%, *Figs 1 and 2*). She was treated with red cell transfusions almost every two weeks and corticosteroids (prednisone 1mg/kg), but with a

further decline of all haematological parameters. The platelet level decreased to 4×10^9/l and the clinical course was complicated by the appearance of haematoma and skin haemorrhagic syndrome.

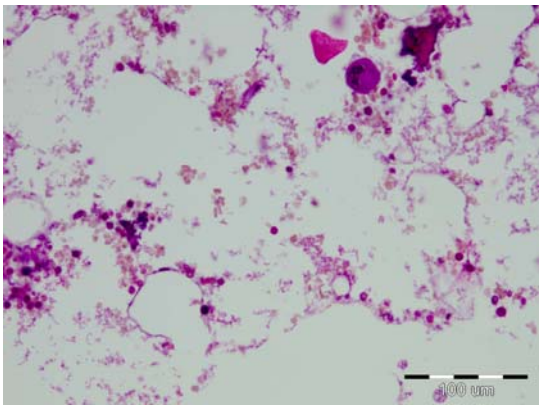

Figure 1 – Hypocellular bone marrow with elements of marrow dysplasia, stained with HE; × 40

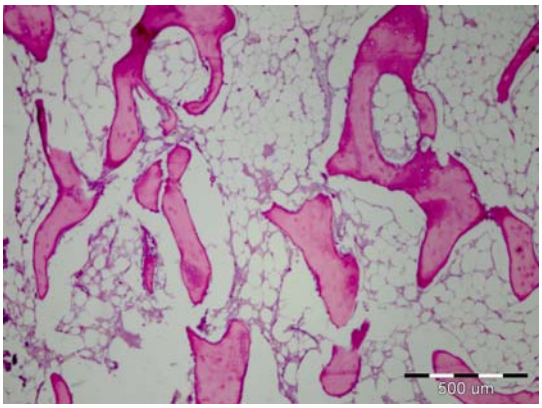

Figure 2 – Hypocellular bone marrow with elements of marrow dysplasia, HE; × 200

In August 2007 she went to a foreign Haematology Clinic in Germany where another bone marrow biopsy was performed. The histological finding was again a hypoclellular form of myelodysplastic syndrome with normal karyotype (46, XX) and IPSS score intermediate 1. They suggested treatment with growth factors and immunosuppressive therapy with ATG and CsA. In the event of treatment failure, further therapy should be allogenic transplantation from human lymphocyte antigen (HLA) from an identical, related or unrelated donor.

Because our patient has only one haploidentical sister and she refused to proceed directly with bone marrow transplantation from a matched unrelated donor, we started with treatment with growth factors (erythropoietin and granulocyte colony stimulating factors-GCSF) and continued with supportive treatment with red cell transfusions and corticosteroid therapy. In the period from June 2007 until June 2008 she received 24 units of packed red blood cell transfusions. Due to the erythropoietin treatment (4000 unit 3 × weekly), her haemoglobin level slowly increased to 100 g/L with a decrease in the number of red cell transfusions to one in two months. But the main problem was persistent and severe thrombocytopenia, resistant to corticosteroid treatment.

In June 2008 we started with immunosuppressive treatment with cyclosporine 200 mg per day and a low dose of prednisone (20mg/day).Treatment with erythropoietin and GSCF continued. Six months after the initiation of the cyclosporine therapy a good partial haematological response was achieved. She no longer required red cell transfusions, treatment with GCSF was stopped and she continued only with CsA (200 mg twice daily), prednisone 5mg per day and erythropoietin (4000 U, 3 × weekly). Her haemoglobin level during the last two years was between 116 and 134 g/L, leukocyte number between 3.7 and 5.1 × 10^9/L with ANC higher than 1.5 × 10^9/L, and platelet count higher than 50 up to 125 × 10^9/L. Control bone marrow biopsy was performed in June 2010 with the histological finding of hypocellular myelodysplastic syndrome but with a marked increase in cellularity compared to the previous biopsies (*Figs 3, 4 and 5*). Her last haemogram in February 2010 showed a haemoglobin level of 124 g/L, leukocyte number 4.1 × 10^9/L with ANC 2.6 × 10^9/L, and platelet count 84 × 10^9/L.

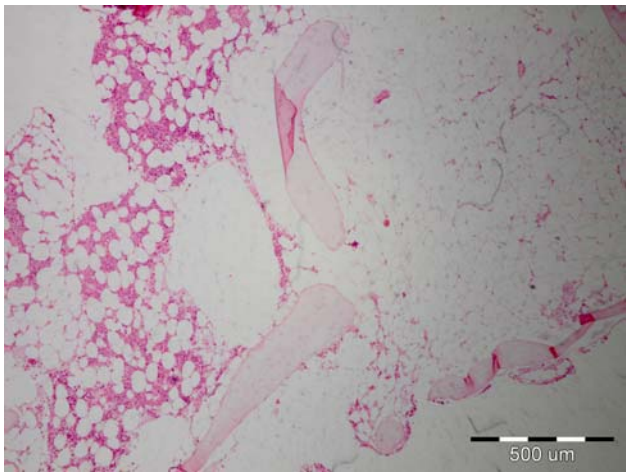

Figure 3 – Hypocellular to normocellular bone marrow with elements of marrow dysplasia, stained with HE; × 40

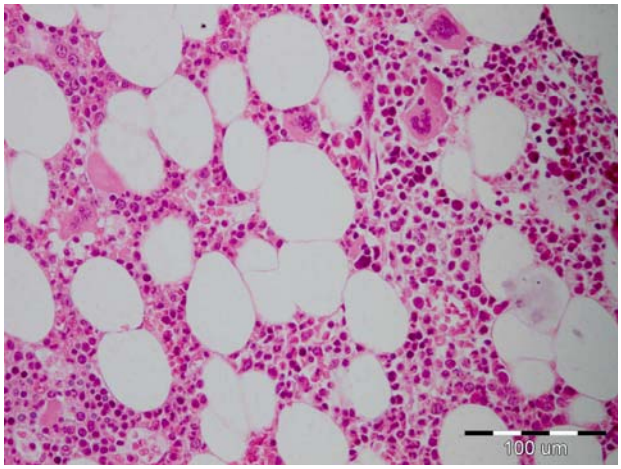

Figure 4 – Hypocellular to normocellular bone marrow with elements of marrow dysplasia, HE; × 200

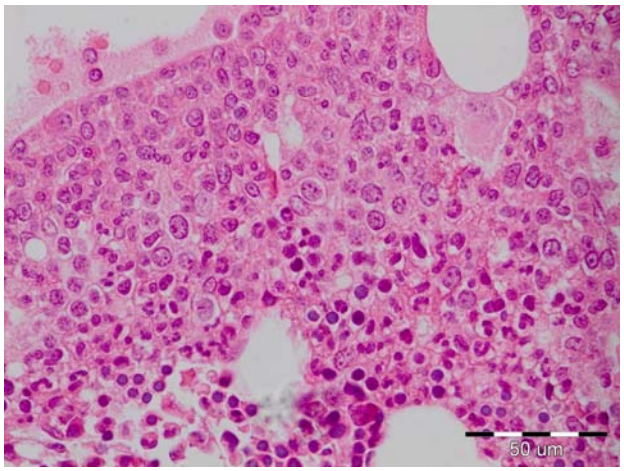

Figure 5 – Normocellular bone marrow with elements of marrow dysplasia, HE; × 400

Discussion

The combination of a hypocellular bone marrow with dysplasia of all three myeloid lineages is an intriguing problem for haematologists and pathologist in terms of classification and treatment. This combination has been descrybed previously as hypocellular, hypoplastic or autoimmune MDS. Some authors classify hypoplastic MDS as AA, while others consider hypoplastic MDS as a

subgroup of MDS [12, 13]. Hypoplastic MDS is probably most accurately categorized as a distinct entity with features of both MDS and AA [12, 15, 16].

There is increasing evidence that immunological dysregulation play an important role in ineffective haematopoesis and progressive cytopenia. Some authors suggest that hypoplastic MDS is caused by an autoimmune reaction similar to that in AA [15, 17]. This theory is supported by the low incidence of karyotypic abnormalities in patients with hypoplastic MDS as opposed to frequently observed karyotypic abnormalities in other clonal stem cell disorders. Patients with hypocellular MDS share an overlap of characteristics with patients with aplastic anaemia. There is skewing of CD4 : CD8 ratios, restricted T-cell receptor Vβ usage together with high plasma levels of tumour necrosis factor-α and interferon-γ indicating a T-cell mediated myelosupression [17–21].

Treatment with immunosuppressive agents like ATG, CsA or both cause clinical improvement (decline and resolution of transfusion requirement, decreased use of haematopoietic growth factors, partial or complete haematological response) in both patients with hypocellular MDS and AA. It has been shown in various studies that patients with hypocellular MDS and low-risk MDS have a higher response rate to immunosuppressive treatment with ATG and CsA and could benefit from this form of treatment, as compared with other patients with MDS [11, 22]. The persistence of dysplastic characteristics of bone marrow after immunosuppressive treatment, which was obvious in our case as well as in other trials, and the apparent need for continuous or repetitive administration of immunosuppressive therapy in patients with hypoplatic MDS, is in contrast to the often durable effect of a single course of ATG and CsA in a patient with AA.

Many trials using antithymocyte globulin or cyclosporine, alone or in combination, have reported responses ranging from zero to 30% in unselected patients [11–18, 22–24]. A recent open-labelled randomized phase III trial by Passweg J.R. *et al*. reported a significant response rate in 29% of patients with MDS treated with ATG+CsA versus suportive treatment only [23]. However, higher response rates were obtained when patients were selected for immunosuppressive treatment based on age, IPPS score, number of months of transfusion dependence and the presence of HLA-DR15 [17, 25].

Other immunosuppressive agents, targeting immune dysregulation in MDS, have also been used in the treatment of patient with MDS in the last few years. Olnes M.J. and Sloand E.M. recently reported the results of a pilot clinical trial [26] and a case report of a 56-year-old woman [27] with hypocellular MDS treated with alemtuzumab (anti CD52 antibody). After treatment with alemtuzumab, her blood cell counts returned to normal and she has remained in complete remission for more than 2 years of follow-up [27]. The overall response rate in this pilot clinical trial was 68% in 31 evaluable patients and the complete response rate was 18% [26].

In conclusion, MDS is remarkably heterogeneous in its clinical presentation, morphology, and risk of progression to acute leukaemia. Recent advances have shown that immune dysregulation contributes to disease pathobiology in selected patients. Our experience with immunosuppressive treatment of a patient with hypocellular MDS is similar to already reported results which confirmed that bone marrow cellularity and low IPSS are important factors predicting response to ATG and CsA. Further studies on the pathogenesis and immunological factors influencing the etiopathogenesis of MDS will identify patients who will respond best to immunosuppressive therapy, as well as establishing the most appropriate IST for each individual.

REFERENCES

1. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, et al. The French-American-British (FAB) Cooperative Group. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982; 51: 189–99.

2. Mufti GJ, Stevens JR, Oscier DG, Hamblin TJ, Machin D. Myelodysplastic syndromes: a scoring system with prognostic significance. Br J Haematol. 1985; 59: 425–433.

3. Guralnik JM, Eisenstaedt RS, Ferrucci L, et al. Prevalence of anaemia in persons 65 years and older in United States: Evidence of high rate of unexplained anemia. Blood. 2004; 104: 2263–2268.

4. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997; 89: 2079–2088

5. Wong R, Shahjahan M, Wang X, et al. (2005) Prognostic factors for outcomes of patients with refractory or relapsed acute myelogenous leukemia and myelodysplastic syndromes undergoing allogenic progenitor cell transplantation. Biol Blood Marrow Transplant; 11: 108–114.

6. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with myelodysplastic syndrome: A study of the cancer and leukemia group B. J Clin Oncol. 2002; 20: 2429–2440.

7. Jadersten M, Montgomery SM, Dybedal I, et al. Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. Blood. 2005; 106: 803–811.

8. van der Bosch J, Lubbert M, Verhoef G, et al. The effects of 5-aza-2'-deoxycytidine (Decitabine) on the platelet count in patients with intermediate and high-risk myelodysplastic syndromes. Leuk Res. 2004; 352: 785–790.

9. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. N Engl J Med. 2005; 352: 549–557.

10. Biesma DH, van den Tweel JG, Verdonck LF. Immunosuppressive therapy of hypoplastic myelodysplastic syndrome. Cancer 1997; 79: 1548–51.

11. Lim ZY, Killick S, Germing U, Cavenagh J, Culligan D, Bacigalupo A, Marsh J, Mufti GJ. Low IPSS score and bone marrow hypocellularity in MDS patients predict hematological responses to antithymocyte globulin. Leukemia. 2007; 21: 1436–41.

12. Nand S, Godwin JE. Hypoplastic myelodysplastic syndrome. Cancer. 1988; 62: 958–64.

13. Tuzuner N, Cox C, Rowe JM, Watrous D, Bennett JM. Hypocellular myelodysplatsic syndromes: new proposals. Br J Haematol. 1995; 91: 612–7.

14. Fohlmeister I, Fisher R, Modder B, Rister M, Schaefer HE. Aplastic anaemia and the hypcellular myelodysplastic syndrome: histomorphological, diagnostic and prognostic features. J Clin Pathol, 1985; 38: 1218–24.

15. Miesher PA, Favre H, Beris P. Autoimmune myelodysplasias. Semin Hematol. 1991; 28: 322–30.

16. Mineishi S, Filippa D, Childs B, Casto-Malaspina H. Hypoplastic myelodysplastic syndrome (MDS): clinical, hematologic and pathologic observations in 36 cases [abstract]. Blood. 1994; 84: 315a

17. Sloand EM, Wu CO, Greenberg P, Young N, Barrett J. Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. J Clin Oncol. 2008; 26: 2505–2511.

18. Kochenderfer JN, Kobayashi S, Wieder ED, Su C, Molldrem JJ. Loss of T-lymphocyte clonal dominance in patients with myelodysplastic syndrome responsive to immunosuppresion. Blood. 2002; 100: 3639–3645.

19. Barrett J, Sauntharajah Y, Molldrem J. Myelodysplastic syndrome and aplastic anemia: distinct entities or diseases linked by a common pathophysiology? Semin Hematol. 2000; 37: 15–19.

20. Martinez-Jeramillo G, Flores-Figueroa E, Sanchez-Valle E, Gutierrez-Espindola G, Gomez-Morales E, Montesinos JJ, et al. Comparative analysis of the in vitro proliferation and expansion of hematopoietic progenitors from patients with aplastic anemia and myelodysplasia. Leuk Res. 2002; 26: 955–963.

21. Young NS, Maciejewski J. The pathophysiology of acquired aplastic anemia. N Eng J Med. 1997; 336: 1365–1372.

22. Killick SB, Mufti G, Cavengah JD, Mijovic A, et al. A pilot study of antithymocyte globulin (ATG) in the treatment of patients with low-risk myelodysplasia. Br J Hematol. 2003; 120: 679–684.

23. Passweg JR, Giagounidis AA, Simcock M, Aul C, et al. Immunosuppressive therapy for patients with myelodysplastic syndrome: a prospective randomized multicenter phase III trial comparing antithymocyte globulin plus cyclosporine with best supportive care-SAKK 33/99. J Clin Oncol. 2011; 29(3): 303–9.

24. Sloand EM, Barrett AJ. Immunosuppression for myelodysplastic syndrome: how bench to bedside to bench research led to success. Hematol Oncol Clin North Am. 2010; 24(2): 331–41.

25. Sauntharajah Y, Nakamura R, Nam JM, et al. HLA-DR15 (DR2) is overrepresented in myelodisplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. Blood. 2002; 100: 1570–1574.

26. Sloand EM, Olnes M, Weinstein B, et al. Alemtuzumab treatment of intermediate-1 myelodisplasia patients is associated with sustained improvement in blood counts and cytogenetic remissions. J Clin Oncol. 2010; 28: 5166–5173.

27. Olnes MJ, Sloand EM. Targeting immune dysregulation in myelodisplastic syndromes. JAMA. 2011; 305(8): 814–9.

Резиме

ИМУНОСУПРЕСИВЕН ТРЕТМАН СО ЦИКЛОСПОРИН-А КАЈ ПАЦИЕНТИ СО ХИПОЛАСТИЧЕН МИЕЛОДИСПЛАСТИЧЕН СИНДРОМ: ПРИКАЗ НА СЛУЧАЈ

Павковиќ М.,[1] Јовановиќ Р.,[2] Петрушевска Г.,[2] Чевреска Л.,[1] Стојановиќ А.[1]

[1]Универзитетска клиника за хематологија, Медицински факултет, Скопје, Р. Македонија
[2]Институт за патологија, Медицински факултет, Скопје, Р. Македонија

Апстракт: Имуносупресивната терапија со антитимоцитен глобулин (АТГ) и/или циклоспорин-А (ЦсА) може да индуцираат хематолошки одговор кај одредена група на болни со миелодиспластичен синдром (МДС), особено кај болните со хипоцелуларна форма на МДС.

Во овој труд реферираме случај со хипоцелуларен МДС лекуван со циклоспорин. Се работи за 54 годишна жена, која се јавила на нашата Клиника поради слабост и тешка панцитопенија. Биопсијата на коска потврди дека се работи за хипоцелуларна форма на МДС. Третманот со циклоспорин-А затпочна една година по иницијалната дијагноза и претходниот супортивен третман. Терапијата со циклоспирин-А доведе до клиничко подобрување на состојбата, многу добар парцијален хематолошки одговор, зголемување на целуларноста на коскената срцевина и намалување на потребата од супортивен третман, особено на трансфузиите на еритроцити.

Нашето искуство покажа дека имуносупресивната терапија со ЦсА и/или АТГ може да бидат алтернатива во третманот на болните со хипоцелуларна форма на МДС, особено за болните за кои не е можна алогената трансплантација, како единствена куративна метода за ова заболување.

Клучни зборови: хипоцелуларен миелодиспластичен синдром, панцитопенија, имуносупресивна терапија, циклоспорин-А.

Corresponding Author:

Pavkovic Marica, MD, MSc.
University Haematology Clinic,
Medical Faculty,
Vodnjanska br.17,
1000 Skopje,
Republic of Macedonia

E-mail:pavkovicm@yahoo.com

Прилози, Одд. биол. мед. науки, XXXII/1 (2011), 313–321

Figure 1 – Hypocellular bone marrow with elements of marrow dysplasia, stained with HE; × 40

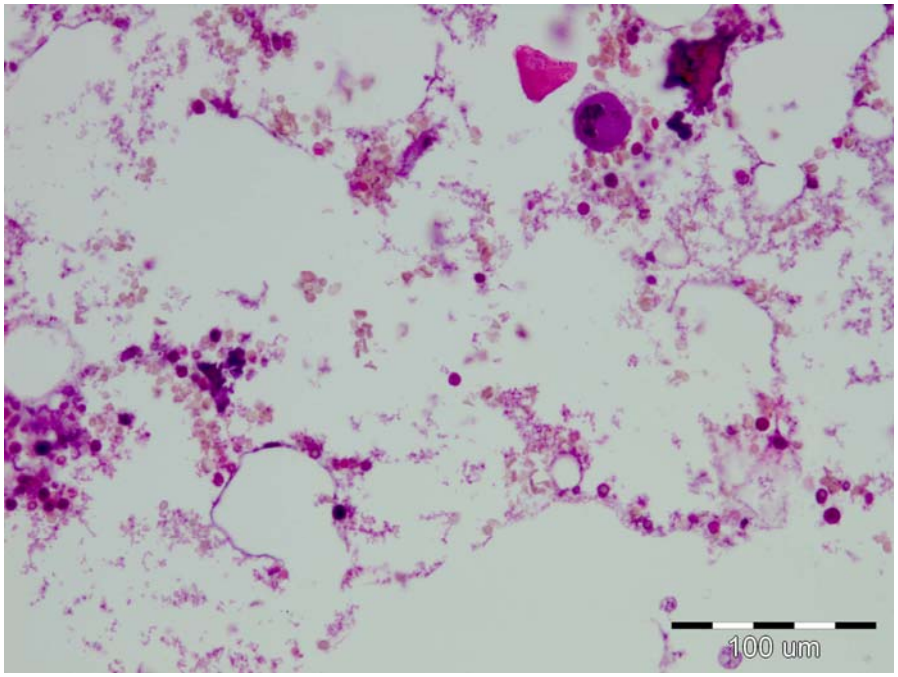
100 um

Figure 2 – Hypocellular bone marrow with elements of marrow dysplasia, HE; × 200

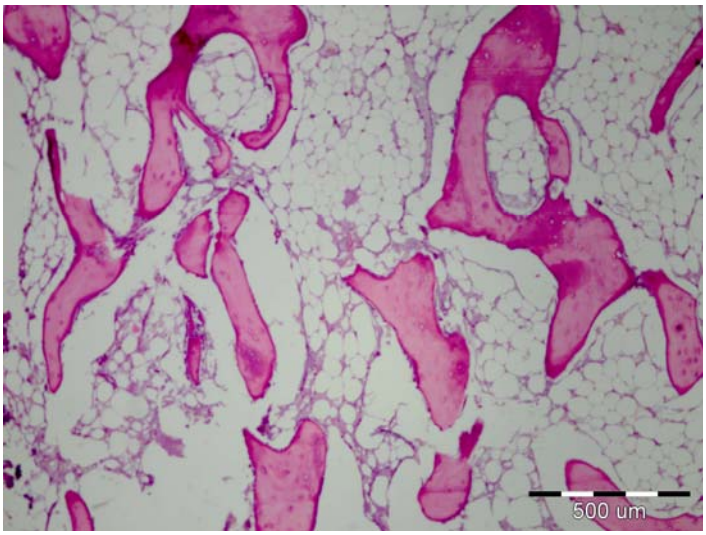

Figure 3 – Hypocellular to normocellular bone marrow with elements of marrow dysplasia, stained with HE; × 40

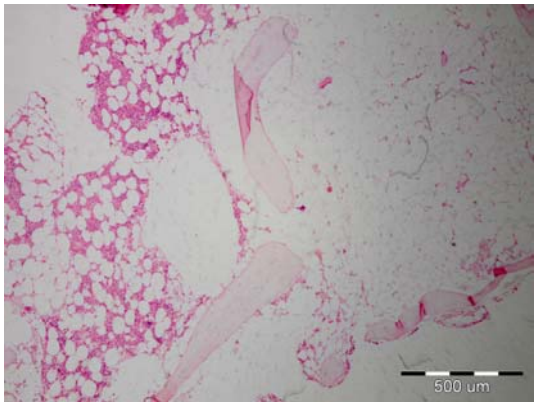

Figure 4 – Hypocellular to normocellular bone marrow with elements of marrow dysplasia, HE; × 200

Figure 5 – Normocellular bone marrow with elements of marrow dysplasia, HE; × 400