Aplastic Anemia as a Cause of Death in a Patient with Glioblastoma Multiforme Treated with Temozolomide

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Background: Standard treatment of glioblastoma multiforme consists of postoperative radiochemotherapy with temozolomide, followed by a 6-month chemotherapy. Serious hematologic complications are rarely reported.
Case Report and Results: The authors present the case of a 61-year-old female patient with glioblastoma multiforme treated with external-beam radiation therapy and concomitant temozolomide. After completion of treatment, the patient developed symptoms of serious aplastic anemia that eventually led to death due to prolonged neutro- and thrombocytopenia followed by infectious complications.
Conclusion: Lethal complications following temozolomide are, per se, extremely rare, however, a total of four other cases of aplastic anemia have been reported in the literature so far.

Key Words: Glioblastoma multiforme · Temozolomide · Aplastic anemia

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Aplastische Anämia als Todesursache bei einer Patientin mit Glioblastoma multiforme nach Temozolomidbehandlung

Hintergrund: Die Standardbehandlung des Glioblastoma multiforme ist die postoperative Radiochemotherapie mit Temozolomid, gefolgt von einer 6-monatigen Erhaltungschemotherapie. Schwerwiegende hämatologische Toxizitäten werden selten berichtet.
Fallbericht und Ergebnisse: Die Autoren präsentieren den Fall einer 61-jährigen Patientin mit Glioblastoma multiforme, die mit externer Strahlentherapie und begleitender Temozolomidchemotherapie in Standarddosierung behandelt wurde. Nach Abschluss der Behandlung zeigte die Patientin Symptome einer schweren aplastischen Anämie, die infolge prolongierter Neutro- und Thrombopenie durch infektiöse Komplikationen zum Tode führte.
Schlussfolgerung: Letale Komplikationen einer Temozolomidchemotherapie sind selten, bislang wurden insgesamt vier Fälle einer aplastischen Anämie in der Literatur berichtet.

Schlüsselwörter: Glioblastoma multiforme · Temozolomid · Aplastische Anämie

Introduction

Glioblastoma multiforme is the most malignant and the most common primary brain tumor in adults. Moreover, this type of brain tumor is characterized by a high degree of genetic and histomorphological variability. Symptoms, which are caused by glioblastoma multiforme, can be divided into general and specific ones due to each tumor type or due to the tumor location and size [7]. Headache is the most common symptom in the majority of patients. It is worsening during sneezing, increased physical activity, or a sudden change in body position. Changes in brain activity appear in one third of patients as epileptic seizures with or without impairment of consciousness. Memory and intelligence deficits are not rare symptoms in these patients. Visual impairment occurs primarily in patients with intracranial hypertension. The basic life functions are at risk, if the primary tumor location is in the brain stem. Swallowing disorders and dysarthria are caused, if the tumor interferes with cranial nerves. Glioblastoma multiforme located in the brain hemispheres disrupts language skills – reading, writing, and voluntary movement. If the tumor is located in the frontal lobe, changes in psyche and behavior appear and memory lapses occur. Unilateral blindness and misunderstanding

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of a written word is the sign of infliction of the occipital lobe. The length of patient's survival with glioblastoma multiforme is dependent on many independent factors – age, neurological status, cognitive functions, the type of tumor, its size and location [2, 3, 8, 13].

The treatment of glioblastoma multiforme is multimodal, i.e., neurosurgical resection, external-beam radiotherapy, systemic chemotherapy, or their combination. The treatment of glioblastoma multiforme is led by a team of experts – a clinical oncologist, a radiotherapist, a neurosurgeon, and a neurologist. This team should then determine the way of cancer therapy in order to ensure the highest possible quality of care and life for the patient.

Case Report

A 61-year-old female patient with a history of arterial hypertension and open-angle glaucoma in the right eye was referred from the Department of Neurosurgery to the Comprehensive Cancer Center on October 16, 2009. She was examined for paresthesias and pain in the left upper extremity lasting for 4 months. Magnetic resonance imaging of the brain showed expansion of 5 cm in diameter in the left frontoparietal area. On October 7, 2009, the patient underwent stereotactic biopsy tumor expansion. Histology proved a high-grade diffuse astrocytoma, but due to the presence of necrosis, the tumor was classified by the pathologist as a glioblastoma multiforme. According to the computed tomography (CT) control of the brain with contrast, there was no complication of stereotactic biopsy. The patient was in a good performance status (ECOG 1) with reduced psychomotor tempo and without neurological deficit.

After 2 weeks from the stereotactic biopsy, the patient was admitted to the Comprehensive Cancer Center to begin a radical external-beam radiotherapy with a 25-mm margin at a dose of 50 Gy in 25 fractions and a boost to the tumor with a 15-mm margin at a dose of 10 Gy in five fractions. During the first days of radiotherapy, it was decided – with regard to the patient's good performance status (ECOG 1) – to start a concomitant chemotherapy with temozolomide at a dose of 75 mg/m^2/day with prophylactic administration of cotrimoxazole. At the beginning and at the end of radiotherapy, the patient was examined by a psychiatrist and a neuropsychologist. The psychiatrist assessed the patient's symptoms, diagnosed a depressive syndrome and recommended to initiate antidepressant treatment (citalopram 20 mg/day). The neuropsychologist examined the patient's neurocognitive functions and diagnosed a mild dementia. Initial examinations of full blood counts and biochemistry laboratory (basic mineralogram, nitrogen catabolite, and liver function tests) were normal. During chemoradiotherapy, the full blood count was controlled regularly once a week. On day 23 from the beginning of concomitant chemotherapy, a decrease of platelet count of 80×10^9/l was detected. There was no clinical manifestation of hemorrhagic diathesis. Concomitant chemotherapy with temozolomide was subsequently stopped and treatment was continued with external-beam radiotherapy. In regard of a very good patient's performance status, the last two fractions of external-beam radiotherapy were given on an outpatient basis with full blood count control after radiotherapy.

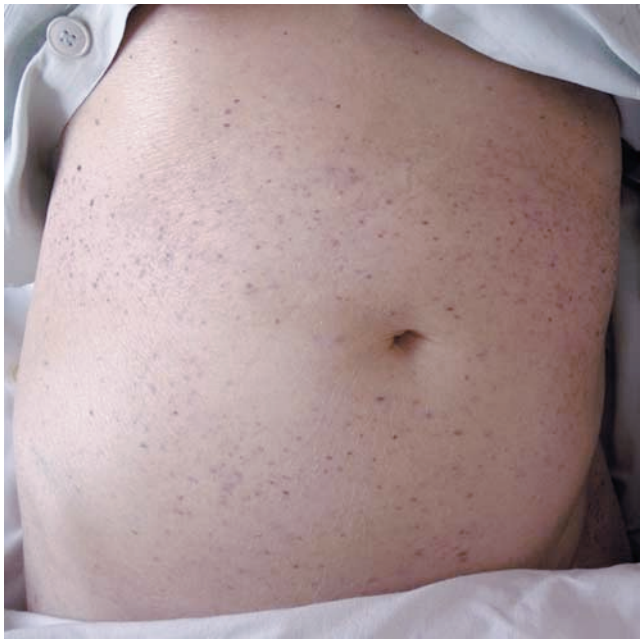

Figure 1. Manifestations of hemorrhagic diathesis with a decline of platelet count to 11×10^9/l (multiple abdominal petechiae).

Abbildung 1. Man ifestationen einer hämorrhagischen Diathese bei einem Rückgang der Thrombozytenzahl auf 11×10^9/l (multiple abdominale Petechien).

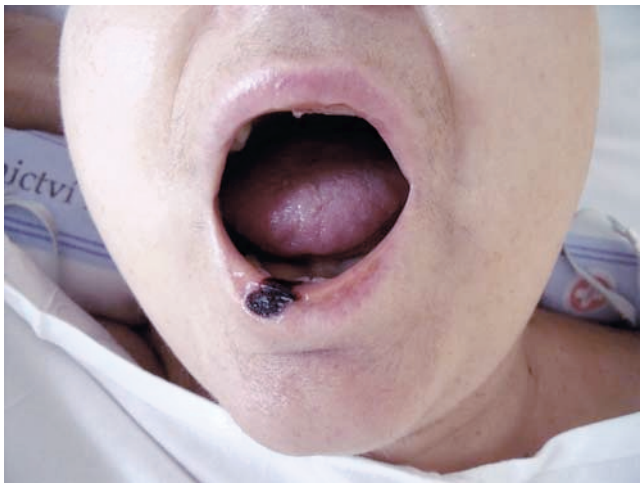

Figure 2. Manifestations of hemorrhagic diathesis with a decline of platelet count to 4×10^9/l (aphthous ulcer bleeding in the lower lip; photo: authors).

Abbildung 2. Manifestationen einer hämorrhagischen Diathese bei einem Rückgang der Thrombozytenzahl auf 4×10^9/l (aphthöse Ulzeration mit Blutung an der Unterlippe; Foto: Autoren).

On December 7, 2009, the full blood count control demonstrated a significant thrombocytopenia (11×10^9/l) with hemorrhagic diathesis signs of multiple petechiae on the legs and trunk and leukopenia (2.2×10^9/l), with the absolute count of granulocytes > 500. This impairment in blood cells count was suspicious in connection with temozolomide treatment. The patient was admitted to hospital due to thrombocytopenia, leukopenia and hemorrhagic diathesis. A control CT scan of the brain with contrast did not prove tumor progression after radiotherapy. Immediately after hospitalization, the regimen provisions (aseptic box) and a selective decontamination (ciprofloxacin and fluconazole) were established. The patient had no stimulation of leukopoiesis. Repeated substitution of platelets was needed because of severe thrombocytopenia with hemorrhagic diathesis (see Figures 1 and 2). On December 11, 2009, severe leukopenia was revealed (blood count 0.34×10^9/l, absolute number of granulocytes < 500), platelet count was $> 20 \times 10^9$/l, and there were no signs of fresh hemorrhagic diathesis, the patient remained afebrile. Leukopoiesis stimulation (filgrastim) was started with regular control of full blood count twice a week. During the whole hospitalization, a short febrile peak without proof of any microbial agent occurred only once.High-resolution pulmonary CT demonstrated homogeneous infiltrates in the upper and lower lobes of the right lung with a pneumonic character. A stepwise change in antibiotic medication was made from ciprofloxacin over cefotaxime and then to meropenem, vancomycin and amikacin. She was put on cotrimoxazole (*Pneumocystis jiroveci* prophylaxis) and acyclovir. During hospitalization, parameters of red blood cell counts were constant. The hemoglobin concentration was in the range of 95–105 g/l. A correction of anemia was performed twice, when the hemoglobin fell to 85 g/l. The values and dynamics of white blood cells, red blood cells and platelets during hospitalization are shown in Figures 3 to 5.

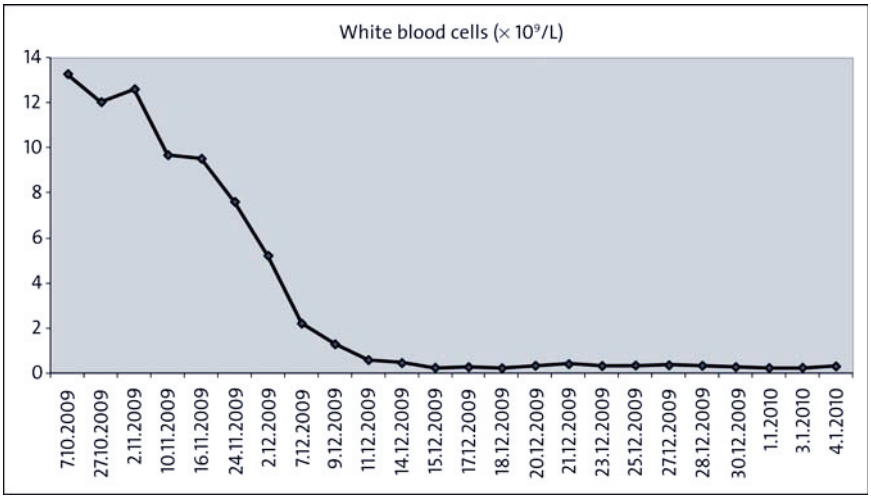

Figure 3. White blood cell values during hospitalization.

Abbildung 3. Leukozytenwerte während des Krankenhausaufenthalts.

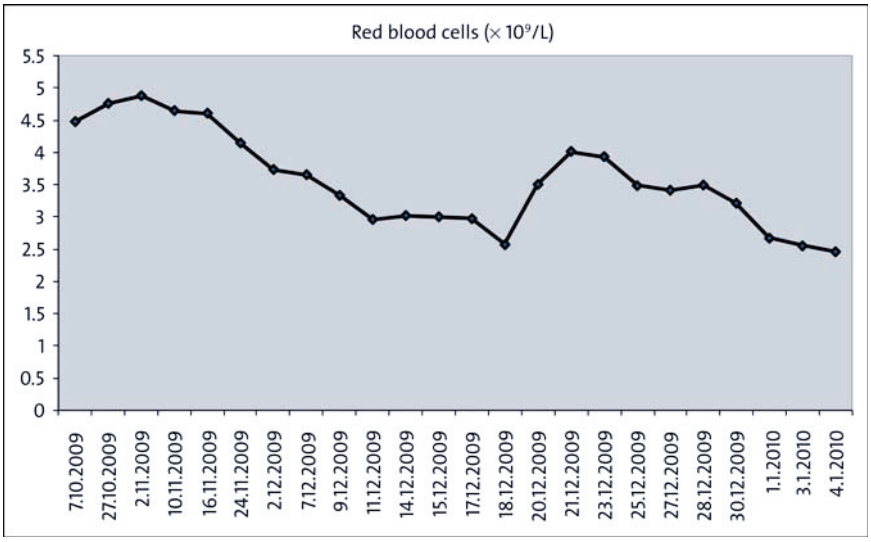

Figure 4. Red blood cell values during hospitalization.

Abbildung 4. Erythrozytenwerte während des Krankenhausaufenthalts.

Due to the prolonged depression of hematopoiesis after chemotherapy with temozolomide and insufficient 3-week leukopoiesis stimulation, the patient underwent sternal puncture and subsequent trepanobiopsy of bone marrow from the iliac crest. A cytological sample was extremely poor in the cells. The erythroid lineage was significantly reduced, but without any signs of dyserythropoiesis. The myeloid lineage was also reduced, with no mature forms present. The predominant cellular elements found in the bone marrow were lymphocytes of mature appearance. A histological examination of the bone marrow showed a severe aplastic anemia. Immunophenotyping flow cytometry of peripheral blood was also performed, which showed an increase in lymphoid cell number, an abnormally increased population of B lymphocytes, and depletion of natural killer cells. T lymphocytes were in the physiological range, but displayed abnormal activation. These findings testified significantly suppressed granulopoiesis (see Figures 6 and 7).

Despite maximum intensive supportive therapy and intensive stimulation of leukopoiesis, there were no signs of repair in hematopoiesis. After 28 days, the intensive supportive therapy was discontinued. The family and the patient were fully informed about the adverse prognosis. By request of the patient and her family, she was discharged from hospital on January 4, 2010, and followed up by palliative ambulatory care of the Comprehensive Cancer Center. After 4 days, the patient died at home from sepsis.

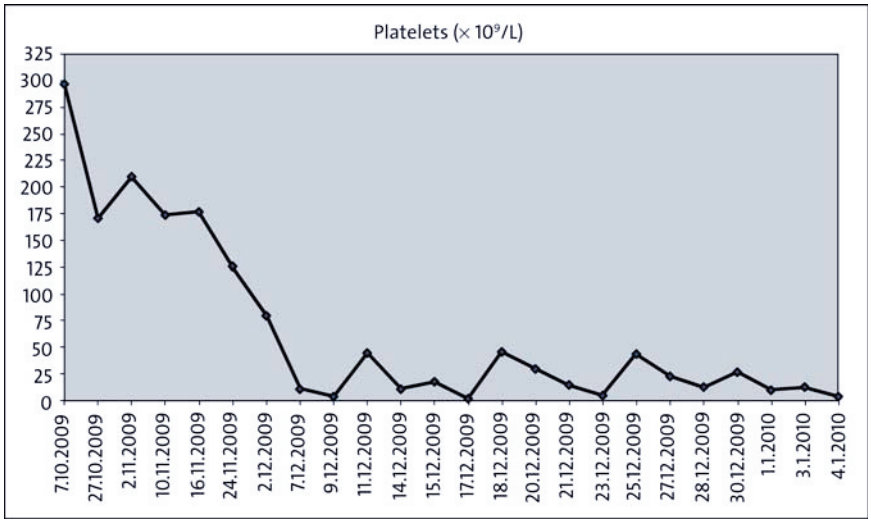

Figure 5. Platelet values during hospitalization.

Abbildung 5. Thrombozytenwerte während des Krankenhausaufenthalts.

Discussion

As already mentioned, all modalities of cancer therapy are used in the treatment of glioblastoma multiforme. The current standard in the adjuvant treatment for glioblastoma multiforme is external-beam radiotherapy with 60 Gy in 30 fractions with concurrent chemotherapy with temozolomide at a dose of 75 mg/m^2/day orally [6, 9, 12]. Temozolomide is a triazen, which, at physiological pH, is undergoing rapid chemical conversion to the active monomethyl-triazenoimidazol-carboxamide. The cytotoxic effect of temozolomide is supposed to be caused by alkylation of DNA at the O^6 position of guanine, followed by alkylation also in position N^7. Subsequently, cytotoxic lesions are explained by mismatch repair of the methyl rest [16]. According to the FDA (Food and Drug Administration), temozolomide is used to treat (1) adult patients with a newly diagnosed glioblastoma multiforme concurrently with radiotherapy and then as a maintenance treatment, (2) adolescents and adult patients with refractory anaplastic astrocytoma. Concomitant administration of temozolomide enhances the effect of external-beam radiotherapy [14], and the administration of temozolomide at the dose of 75 mg/m^2 is considered to be safe. However, temozolomide is also known to have side effects, the most common being nausea, vomiting, constipation, anorexia, alopecia, headache, fatigue, seizures, rash, neutropenia, lymphopenia, and thrombocytopenia.

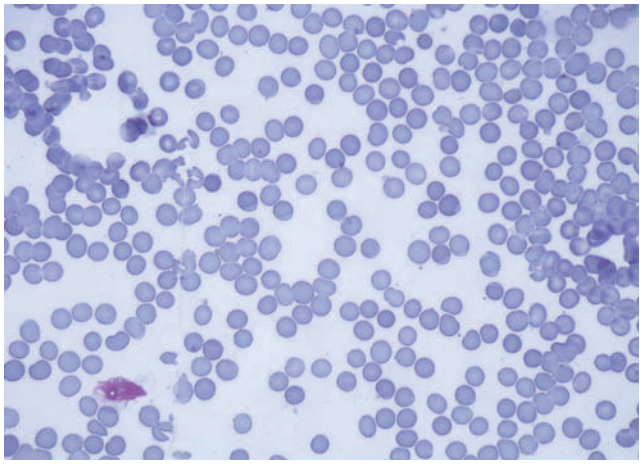

Figure 6. Sternal puncture – cytology staining poor in cells.

Abbildung 6. Sternalpunktion – zytologische Färbung zellarm.

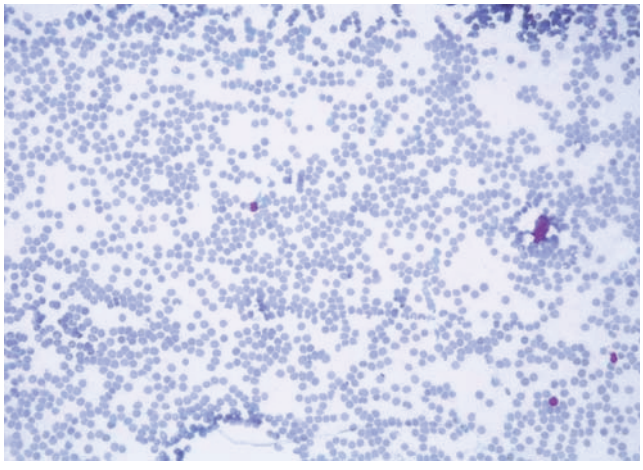

Figure 7. Bone marrow aspiration from the iliac crest – cytologically, extremely poor in cells.

Abbildung 7. Knochenmarkaspiration aus dem Beckenkamm – zytologisch extrem zellarm.

One of the clinically most relevant side effects of temozolomide is hematotoxicity.

Severe thrombocytopenia occurs in 4–19% of patients with glioblastoma multiforme treated with temozolomide. Neutropenia is seen in 8% of patients, and the incidence of leukopenia in patients treated with temozolomide has been described to be up to 11% [5, 10, 12]. In connection with temozolomide treatment, an aplastic anemia has already been recorded [1, 4, 11, 15]. In our case, the patient developed severe aplastic anemia in association with short-term temozolomide treatment. Despite maximum intensive supportive therapy (3-week stimulation of leukopoiesis) of aplastic anemia, deterioration of hematopoiesis was irreversible, which also resulted in death from sepsis. We believe that aplastic anemia is not only the result of temozolomide activity. Often, there are several factors such as concomitant prophylactic administration of cotrimoxazole, anticonvulsants or H_2 blockers, which can cause thrombocytopenia.

Conclusion

Our case report points to the need for regular monitoring of full blood count in patients with glioblastoma multiforme treated with temozolomide in order to adequately react to the possible danger of fatal hematologic toxicity. It also indicates the fact that the hematologic toxicity of temozolomide may lead to the extension of necessary hospitalization time, or outpatient treatment may necessitate emergency hospitalization. In these individual cases, glioblastoma multiforme treatment is considered beneficial with regard to quality of life.

Acknowledgments

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((Copyeditorial remarks:
- 1: Some references were brought in alphabetical order and their numbers given in the text changed accordingly
- 2: Suggested change: "... radiotherapy with a 25-mm margin at a dose of 50 Gy in 25 fractions and a boost to the tumor with a 15-mm margin at a dose of 10 Gy in five fractions."
- 3: Please check wording; suggested change: "... count to 80×10^9/l"
- 4: Suggested change: "... radiotherapy were given on an outpatient basis"
- 5: Please check unclear/incomplete text
- 6: Suggested change: "Immediately after hospitalization,"
- 7: Suggested change: "The patient had no"
- 8: Please check if insertion of "count" required
- 9: Suggested change: "the patient was still afebrile." or "the patient remained afebrile."
- 10: Suggested change: "High-resolution pulmonary CT demonstrated homogeneous infiltrates"
- 11: Suggested change according to current nomenclature: "*Pneumocystis jiroveci*"
- 12: Please check wording [pleonasm]; suggested change: "... twice, when the hemoglobin concentration fell to 85 g/l." or "twice after a decrease of hemoglobin concentration to 85 g/l."
- 13: Please check unclear wording
- 14: Please check wording; suggested change: "The myeloid lineage was also reduced, with no mature forms present." or "The myeloid lineage was also reduced, with absence of mature forms."
- 15: Suggested change: "... also performed, which showed an increase in lymphoid cell number, an abnormally increased population of B lymphocytes, and depletion of natural killer cells."
- 16: Suggested change: "range, but displayed abnormal activation."
- 17: Suggested change: "As already mentioned, all modalities of cancer therapy are used in the treatment of glioblastoma multiforme."
- 18: Suggested change: "The current standard in the adjuvant treatment for glioblastoma multiforme is external-beam radiotherapy with 60 Gy in 30 fractions and concurrent"
- 19: Suggested change: "The cytotoxic effect of temozolomide is supposed to be"
- 20: Please check if better "mismatch repair"
- 21: Suggested change: "However, temozolomide is also known to have side effects, the most common being"
- 22: Suggested change to avoid repetition: "... anemia in association with"
- 23: Please check unclear wording ["reparations ... appear irreversible"?]
- 24: Please check wording; suggested change: "which also resulted in death from sepsis."
- 25: Suggested change: "Often, there are several factors such as concomitant prophylactic administration of cotrimoxazole, anticonvulsants or H_2 blockers, which can cause thrombocytopenia."
- 26: Suggested change to avoid repetition: "or outpatient treatment may necessitate"
- 27: Please check if really "forced" or rather "urgent" or "emergency" meant
- 28: Please check wording; suggested change: "In these individual cases, glioblastoma multiforme treatment is considered beneficial with regard to quality of life."
- 29: Please check wording; suggested change: "... diathesis with a decline of platelet count"
- 30: Please check unclear wording; possibly "cytological staining poor in cells"
- 31: Please check unclear wording; possibly "zytologische Färbung zellarm"
- 32: Please check if this should read "iliac wing" or – according to text – "iliac crest"
- 33: Please check unclear wording; possibly "cytologically, extremely poor in cells"
- 34: cf. remark 32: ok. or rather "aus dem Beckenkamm" according to text))