Diplomarbeit

The role of tyrosine kinase inhibitors in the treatment of inoperable desmoid tumours

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Daniela Hetzel

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Graz, am …….. (Unterschrift)

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Daniela Hetzel

List of Contents

Abbreviations

ABL	Abelson Protooncogene
APC	Adenomatous Polyposis Coli Gene
ARG	Abelson Related Gene
ATP	Adenosine Triphosphate
BCR	Break Point Cluster Region
CD 34	Stem Cell Factor Receptor
C-KIT	CD 117, Stem Cell Factor Receptor
CNS	Central Nervous System
COX-2	Cyclooxygenase 2
DNA	Deoxyribonucleic Acid
EMA	Endomysial Antibodies
FAP	Familial Adenomatous Polyposis
GIST	Gastrointestinal Stromal Tumours
GS	Gardner's Syndrome
Gy	Gray
IGFR	Insulin-like Growth- Factor Receptor
IPAA	Ileal Pouch- Anal Anastomosis
M- CSFR	Macrophage- Colony Stimulating Factor Receptor
mRNA	Messenger Ribonucleic Acid
MUTYH	mutY Homolog E. coli, Human gene
NSAID	Nonsteroidal Anti- Inflammatory Drugs
PCR	Polymerase Chain Reaction
PDGFR	Platelet Derived Growth Factor Receptor
RNA	Ribonucleic Acid
S-100 Protein	A type of low molecular weight protein
SMA	Smooth Muscle Antibodies
WNT	Wingless Int 1, describes a complex network of proteins most well known for their roles in embryogenesis and cancer

List of Figures

List of Tables

Abstract

Desmoid tumours are rare neoplasms that evolve from musculoaponeurotic stromal elements. The term desmoid originates form the Greek word “desmos”, meaning band or tendon-like and was first described in the 1800s to characterize tumours with tendon-like consistence. The tumours are classified pathologically as aggressive fibromatosis. Desmoid tumours arise sporadically or in patients with FAP (familial adenomatous polyposis syndrome) or Gardner’s-syndrome.

Aggressive fibromatoses are divided into intraabdominal and extraabdominal forms. Previous traumata as well as surgical intervention and estrogen exposition may induce the occurrence of this tumour.

The pathology is multifarious and contingent on the size and the localization of the tumour.

Due to the fact that desmoid tumours tend to have high rates of relapses following surgical resection, medical therapy for recurrent and unresectable aggressive fibromatosis with tamoxifen, nonsteroidal antiinflammatory drugs or chemotherapy can be used.

Recent reports showed that aggressive fibromatosis may respond to treatment with imatinib mesylate (Glivec). Imatinib mesylate is normally used in patients who suffered from chronic myeloid leukaemia and gastrointestinal stromal tumours (GIST).

Imatinib mesylate shows inhibitory activity against tyrosine kinase including PDGFR-alpha and PDGFR- beta and c- kit subtype, however recent evidence suggested that even patients with C-KIT negative tumours may benefit from the therapy with inhibitors against the tyrosine kinase (Glivec).

In this diploma thesis I want to present the case of a young male patient who has received imatinib mesylate for an inoperable desmoid tumour over a period of four years. Growth arrest of the tumour and intralesional necrosis was observed lasting more than 4 years on treatment. Sustained tumour response could be documented after cessation of treatment during an observation period of 12 months

Zusammenfassung

Desmoide Tumoren gehören zu der Kategorie der Weichteiltumoren und entstehen aus Zellen der muskulären Membranen (Aponeurosen). Der Ausdruck „Desmoid“ leitet sich von dem griechischen Wort „Desmos“ ab, das für „Band“ steht, und wurde das erste mal 1800 zur Beschreibung von Tumoren, die eine bandartige Konsistenz aufweisen, angewandt. Diese Tumoren werden pathologisch als aggressive Fibromatosen klassifiziert. Desmoide Tumoren können sporadisch oder im Zusammenhang mit der Familiären Adenomatösen Polyposis (FAP), beziehungsweise dem Gardner- Syndrom, auftreten.

Je nach Lage im Körper unterscheidet man die intraabdominalen von den extraabdominalen Formen.

Verletzungen chirurgischer Art, beispielsweise durch Operationen oder durch Traumata, werden oft als mögliche Ursache für das Auftreten des Tumors beschrieben. Die Pathologie dieser Tumoren ist sehr vielfältig und abhängig von der Größe und der Lokalisation des Tumors.

Aufgrund der Tatsache, dass diese Tumoren eine hohe Rezidivrate nach operativen Eingriffen aufweisen, wird meist eine medikamentöse Therapie mit Tamoxifen, Nichtsteroidalen Antiphlogistikern und Chemotherapeutikern eingeleitet. Neue Studien zeigten, dass Imatinib (Glivec®), das ursprünglich zur Behandlung der chronisch myeloische Leukämie und der gastrointestinalen Stromatumoren eingesetzt wird, auch bei diesen Tumoren zur Anwendung kommen kann. Imatinib führt zu einer Hemmung der Tyrosinkinase, dem PDGFR –alpha/beta und der C- Kit Subtypen. Jüngste Erkenntnisse zeigen, dass auch C-kit negative Tumoren von dieser Behandlung profitieren.

In dieser Diplomarbeit möchte ich einen Fall aufzeigen, indem ein junger männlicher Patient, der an einem inoperablen desmoiden Tumor leidet, erfolgreich mit Glivec über einige Jahre behandelt wird. Es konnte gezeigt werden, dass unter der Therapie mit Glivec ein Wachstumsstillstand und eine intralesionären Nekrose des Tumors erreicht wurde. Auf Wunsch des Patienten wurde die Therapie ausgesetzt und über einen Zeitraum von zwölf Monaten zeigten sich keine Veränderungen hinsichtlich der Größe und der Lokalisation des Tumors.

1 Introduction

Desmoid tumours are rare neoplasms that evolve from musculoaponeurotic stromal elements. “The term desmoid originates from the Greek word “desmos”, meaning band or tendon-like and was first applied in the 1800s to describe tumours with a tendon-like consistency.”[1]These tumours are classified as semi malignant because they grow locally aggressive but they have no metastatic potential.

“The incidence of desmoid tumors has been shown to be between 2 and 4 cases per 1 million people per year in Finland. They constitute about 3.5% of all fibrous tissue tumors and 0.03% of all neoplasm.”[2]

The pathogenesis of desmoid tumours is still unclear but trauma, endocrine and genetic factors seem to play a decisive role in the development of these tumours.

Aggressive fibromatosis are often found in patients who suffer from the Familial Adenomatous Polyposis Syndrome (FAP). FAP is an autosomal dominantly inherited disease, characterized by the development of hundreds of thousands adenomatous colorectal polyps.
Fibromas, epidermal and sebaceous cysts and osteomas in connection with the Familial Adenomatous Polyposis Syndrome were first described as Gardner’s Syndrome.

“Because 55-72% of aggressive fibromatosis are located within the mesenteric, their extensive proliferative nature may lead to intestinal or ureteric obstruction or small bowel infarction. “[2]
Due to this fact the tumour is able to compress vital structures and can lead to death.

1.1 Occurrence and History

Desmoids occur in three general locations:

1. “The extremities (commonly around limb girdles or proximal extremity)

2. The abdominal wall (commonly found in women, especially during and after pregnancy)

3. The bowel wall and mesentery (often associated with Familial Adenomatous Polyposis)”[3]

Aggressive fibromatosis are divided into intraabdominal or extraabdominal forms
This is due to differences in occurrence of clinical symptoms. Extraabdominal forms appear as painless or minimally painful mass with a slow growth rate. Intraabdominal forms often cause intestinal obstruction, mucosal ischemia or functional impairment of vital structures and organs.

As noted above desmoid tumours arise sporadically or in patients with FAP or Gardner Syndrome.
Trauma, earlier surgical intervention and estrogen exposition may support the occurrence of these tumours.

The pathology is multifarious and contingent on the dimension and the localization of the tumour. Multicentric or multifocal development of desmoids tumors is the reason for a high rate of relapse. Medical therapy for recurrent and unresectable aggressive fibromatosis with tamoxifen, nonsteroidal anti-inflammatory drugs or chemotherapy can be used.

Recent reports showed that desmoids respond to treatment with imatinib mesylate (Glivec). Imatinib mesylate shows inhibitory activity against tyrosine kinase including PDGFR α and PDGFR β and C-KIT subtype, however recent

recognitions demonstrated that even patients with C-KIT negative tumours benefit from the therapy with inhibitors against the tyrosine kinase (Glivec).
Now the epidemiology, clinical presentation and treatment of desmoid tumours will be discussed:

1.2 Epidemiology

"Desmoid tumors are uncommon; they account for about 0.03 percent of all neoplasms, and less than 3 percent of all tissue tumors".[1] "The incidence is estimated at two to four persons per million per year, with relative peaks in incidence between 6 and 15 years of age and between puberty and age 40 years in women."[4]

Desmoid tumours emerge uncommonly in the young and in the elderly. In women they can be found more frequently than in men. There is no significant correlation to race or ethnicity. The occurrence of desmoid tumours is higher in patients who suffered from FAP.
"Desmoids affect from 4 to 20 percent of patients with FAP."[1]

Despite this data the development of this tumour is still ambiguous. Just recently "molecular studies of X-chromosome inactivation have confirmed that these lesions are the result of a clonal process, establishing that desmoid are neoplasms and not the product of an intense inflammatory fibrous reaction. "[3]

Confounding factor is that many studies have mixed intra- and extraabdominal forms and they combined primary and recurrent tumours. On the basis of this fact you can find conflicting reports regarding the biology and management of these tumours.
For this reason the molecular aetiology of aggressive fibromatosis remains to be elucidated.

1.3 Histology

Desmoid tumours appear as infiltrative but well-differentiated tumours which are locally aggressive.

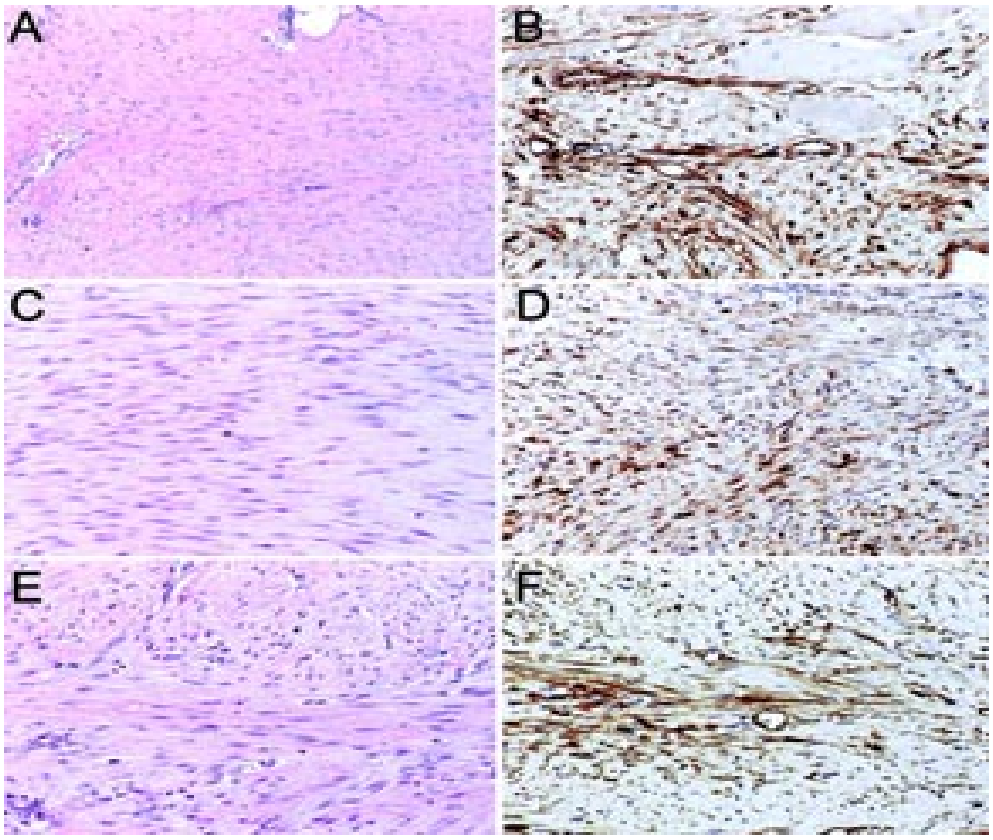


Figure 1: A and **B**, deep fibromatosis (desmoid tumor), hematoxylin and eosin (H&E) (**A**) and β-catenin immunohistochemistry (**B**). Note that most of the nuclei (estimate: 80%) show β-catenin accumulation, whereas the endothelial cell nuclei and infiltrated skeletal myocyte nuclei are negative. **C** and **D**, plantar fibromatosis. These superficial fibromatoses are frequently mitotically active (**C**, H&E). On the immunohistochemical preparation (**D**), scattered nuclei (estimate: 10 to 15%) display nuclear β-catenin accumulation, and cytoplasmic staining is focally present. No mutations were identified in either the β-catenin or *APC* genes. **E**and**F**, infantile digital fibromatosis showing the characteristic cytoplasmic inclusions (**E**, H&E). Scattered nuclei (estimate: 10 to 15% in this field) also show β-catenin accumulation by immunohistochemistry (**F**), although no mutations were identified in either the β-catenin or *APC* genes.[5]

"Histologically they are characterized by small bundles of spindle cells in an abundant fibrous stroma. "[1]

The fibroblast can be found at the periphery of the lesion, the cellularity is low and there exist only a few mitotic figures. Necrosis cannot be found. Thus they are easy to distinguish from sarcomas.

The stroma is collagenous to myxoid and contains a variable amount of slit like vessels, sometimes with a focal perivascular lymphocytic infiltration.

Immunohistochemistry may support the histologic diagnosis. “The spindle cells usually stained for vimentin and smooth muscle actin and nuclear beta- catenin but are generally negative for desmin, cytokeratins, and S-100.”[6]

1.4 Trisomy 8 and 20

“Non-random clonal chromosomal changes, particularly trisomy 8 and 20 occur in one-third or more of sporadic desmoid tumors.”[1]

The relevance of this genetic alteration is still unknown but tumours which show a trisomy 8 or 20 are associated with higher rates of relapses.
Individual trisomies can often be found in mesenchymal tumours. They often occur in benign fibrous lesions, including Dubuytren’s contracture, plantar fibrosis, Peyronie’s disease, Carpal Tunnel Syndrome and infantile fibrosarcoma.
In hematologic malignancies frequently trisomy 8 can be found but in non-fibrous solid tumours this kind of trisomy doesn’t occur very often.

2 Causes of Desmoid Tumours

2.1 Familial Adenomatous Polyposis

Familial adenomatous polyposis is characterized by various adenomatous colorectal polyps. The diagnosis includes:

1. “A cancer that occurs at a usually young age compared with its usual presentation

2. The development of multiple tumors in a single organ, or bilateral development in tumors in paired organs

3. The development of more than one primary tumor of any type

4. A family history of cancer of the same or a related type in first-degree relatives

5. Cancer occurring in an individual or within a family with congenital anomalies or birth defects

6. A high rate of cancer occurrence in the family”[7]

The causes of desmoid tumours are unclear. Trauma, estrogen exposition or genetic reasons may contribute to the occurrence of these tumours.
“Familial adenomatous polyposis and its variants - Turcot´s Syndrome (FAP associated with brain tumours), Gardner’s Syndrome (FAP with associated extraintestinal manifestations), and attenuated Familial Adenomatous Polyposis – are autosomal dominant diseases caused by mutation in the adenomatous polyposis coli (APC) gene.”[1] APC is a tumour suppressor gene and prohibits the expansion of tumours.

So this tumour suppressor gene inhibits the oncogenic protein beta – catenin. “However, other tumour-suppressor functions of APC may be related to cell adherence and cytoskeleton organization. “[8]

In some cases a so-called MUTYH gene mutation can be found. This gene is able to encode the DNA repair enzyme MUTYH glykosylase. “During normal cellular activities, guanine sometimes becomes altered by oxygen, which caused it to pair with adenine instead of cytosine.”[8] In this case MUTYH glykosylase repairs the damaged DNA during DNA replication. If this mechanism is defective, DNA errors may occur and initiate tumourigenesis. In this case the clinical symptoms are equal to those in patients with APC mutation.

2.2 Gardner’s Syndrome

Gardner’s Syndrome is a variant of Familial Adenomatous Polyposis and was first described in the early 1950´s. After discovering the adenomatous polyposis gene (APC) – the gene which is responsible for the appearance of the Familial Adenomatous Polyposis - it turned out that both FAP and Gardner’s Syndrome arose from APC mutation. “Gardner’s Syndrome is generally linked to band 5q21, the adenomatous polyposis coli locus. FAP and Gardner’s syndrome are believed to be variants of the same conditions.”[9]

It is very difficult to separate Gardner’s Syndrome from FAP. “Estimates for the combined syndromes vary from 1 in 6850 to 1 in 31,250 people. “[10]

It is also an autosomal dominant disease and it consists of the following symptoms:

1. Gastrointestinal polyps

2. Multiple osteomas

3. Skin and soft tissue tumours (including epidermoid cysts and benign tumours)

4. Dental abnormalities

Due to the fact that polyps incline to malignant transformation, an early diagnosis is fundamental.

2.3 Pregnancy

Most frequently desmoid tumours appear in women before menopause. But they also tend to occur in women during or following pregnancy. If so aggressive fibromatosis are characterized by an abdominal mass separated from the uterus.
There also exists the possibility that the tumour degenerates during the menopause.
In conclusion you can say that the existence of hormone receptors in tumour cells may have an influence on the appearance of desmoid tumours.

2.4 Trauma

Injuries caused by accident or operation may also have an influence on the occurrence of desmoid tumours. As an example, many studies described the appearance of desmoid tumours in the range of the scar tissue, for example after laparoscopy or after inserting silicon breast implants.

3 Different Classifications of Desmoid Tumours

Desmoid tumours are divided into intraabdominal and extraabdominal forms. Extraabdominal aggressive fibromatosis are predominately found in the extremities, neck, head and in the chest. Intraabdominal tumours tend to occur most frequently in the abdominal cavity (mesentery).

Extraabdominal desmoids usually occur sporadic and are treated with local therapy. Although desmoids are inherently benign, they have a high rate of recurrence if they are treated with surgery alone. Patients who suffer from multiple local relapses despite adequate treatment are debated for systemic therapy.

“In contrast, intraabdominal desmoids, particularly those arising in the setting of FAP, are often unresectable because they are characterized by diffuse infiltration of the mesentery.”[1] These patients are considered for systemic therapy because recurrences become more frequent and aggressive with each surgical intervention.

4 Clinical symptoms, Diagnosis and Treatment of Desmoid Tumours

4.1 Clinical Presentation

Table 1: Anatomical location of the desmoid tumours [11]

Desmoid subtype	Patients	Mean age at Diagnosis, years	male	female
Extra – abdominal	47	30	19	28
Abdominal	22	34	4	18
Intra – abdominal	13	53	8	5
Infantile	3	4	1	2
Total	85	34	32	53

Aggressive fibromatosis develop as a painless or minimal painful mass. They are characterized as slow growing tumours but large desmoids can cause deformity, functional impairment and death when vital organs are affected.

Desmoid tumours can be found at any body site but three main anatomical locations are described: extraabdominal, abdominal and intraabdominal. “In patients with FAP, abdominal desmoids predominate. In non-FAP-associated cases, the most commonly involved areas are the shoulder girdle, hip-buttock region and the extremities, where the location is usually deep in the muscle or along fascial planes.”[6]

Desmoid tumours may occur multifocal on an extremity but they uncommonly manifest at different regions in the same patient.

Intraabdominal desmoid tumours may cause:

1. Intestinal obstruction
2. Mucosal ischemia
3. Functional deterioration
4. Ileoanal anastomose
5. Pain
6. Rectal bleeding

Important to mention is that intraabdominal desmoid tumours can manifest at any body site.

“Superficial desmoids tend to be less aggressive than deep desmoids (abdominal, extraabdominal, and mesenteric).”[12]

In the case report the tumour of the patient occurred sporadically. An MRT-scan was performed and showed a large desmoid tumour of the right pleural cavity. Although surgical resection was performed local recurrence was noted on magnetic resonance imaging four months later.

4.2 Diagnosis

Biopsy

Surgery may be required to get a biopsy for an adequate diagnosis. After that a pathologist analyzes the cells under a microscope to determine if desmoid cells are present. “Incisional biopsy is often preferred over a needle biopsy because of the need to distinguish between a benign and malign process with very high confidence.”[1]

Ultrasound

Ultrasound can be used to demonstrate the existence of a tumour. It is a non-invasive and painless procedure and often it is the first examination of the lesions concerning the torso or extremity.

Computed Tomography (CT) Scan

Computed Tomography Scans (CT) create two-dimensional images of the body. They are able to show if the tumour has invaded other structures or organs.

You can distinguish different kinds of computed tomography scans, including:

1. Spiral CT

2. Multi-detector row spiral CT

Spiral CT scans create high-resolution two-dimensional images in contrast to multi-detector row spiral CT scans, which create high-resolution three-dimensional images.
If the tumour mass is solid, “CT or MRI are needed to determine adherence to adjacent structures and respectability.”[1]

Magnetic Resonance Imaging (MRI) Scan

Magnetic Resonance Imaging (MRI) technology utilizes magnetic fields and radio waves and provides accurate information about the tumour. Although desmoids can be adequately evaluated by CT, MRI is preferred for definition of pattern and expansion of the malignancy.

Positron Emission Tomography (PET) Scans

It is a non-invasive nuclear medicine medical imaging technique which creates a three-dimensional image. It is able to illustrate the functional processes of the body.

Sometimes it is very useful in the diagnosis of desmoid tumours but as mentioned before CT and MRI are better inclined to evaluate the pattern and the expansion of the tumour.

4.3 Treatment

Surgery

"Because of their locally infiltrative nature, desmoid tumours are treated by resection with wide margin when medically and technically feasible."[1]
The standard surgical goal is the complete resection of the tumour to achieve negative microscopic margins but this is often limited by anatomic boundaries.
In case that desmoids are benign tumours, it is very important to derive tumour-free margins to minimize major morbidity.
Intraabdominal tumours are more difficult to operate than extraabdominal and abdominal wall tumours. In this case medical therapy may be taken into consideration as a first-line option, mainly for progressing tumours that infiltrate the mesentery, vessels or organs.
The high recurrence rate of aggressive fibromatosis after surgery, even after aggressive resection with wide margins, is a big problem. These tumours are able to start growing again within a few months after resection and in this case salvage therapy with radiation therapy and/or repeat excision might be successful.
If intraabdominal desmoids accrue in connection with the Gardner's Syndrome the prognosis will be very poor, because they have a higher recurrence rate and they tend to occur in multiple places. "Morbidity after attempted resection, which often includes removal of part of the small intestine, is substantial."[1]

Radiation Therapy

"The role of radiotherapy in desmoid tumour management is also controversial."[13]
It is the primary therapeutic option for patients who are not suitable for surgery, who do not approve surgery, and for patients that have a high risk of morbidity.
If this kind of therapy is used it is very important to utilize the accurate energy source and dose. The common dose of radiation therapy is "50 to 60 Gy in six to seven weeks at 1.8 to 2 Gy per fraction."[1]

If higher doses are used it will have no influence on the recurrence rate and it will be associated with a higher rate of complications. It is very important to balance risk and benefit.

Postoperative Radiation Therapy

Postoperative radiation therapy should only be conducted if the patient shows a positive resection margin. But a positive resection margin is not always associated with higher recurrence rate. Many cases show an increased rate of relapse because they didn't get radiation therapy or adequate salvage therapy at the time of surgery.
However, postoperative irradiation should be employed if microscopically positive margins or macroscopic residual disease after resection of the tumour is documented."[1]

It is also possible to use neoadjuvant therapy to reduce the rate of local relapses. Radiotherapy with or without chemotherapy can be utilized.

Systemic Therapy

If patients suffer from extraabdominal desmoid or multiple recurrences in spite of adequate local therapy, they should be considered for systemic therapy.
Other indications include:

1. inoperable tumours

2. Intraabdominal tumours, particularly those associated with FAP.

In consideration of the fact that aggressive fibromatosis tend to grow locally infiltrative and can be deadly if the tumour destroys vital structures and organs, it is imperative to treat these tumours immediately, especially when they cause

symptoms. In this case an early systemic therapy is able to minimize serious consequences.

Two types of systemic therapy can be distinguished: Cytotoxic and non- cytotoxic. Cytotoxic systemic therapy is the first-line therapy for patients with rapidly growing tumours or for those who are afflicted with symptoms, such as pain, functional deterioration or paralysis.

Noncytotoxic Systemic Therapy

Evidence exists that the growth rate of aggressive fibromatosis might be responsive to activation of the COX-2 pathway or to sex hormones. Particularly in patients who are unsuitable for surgery or radiation therapy, therapy with anti-estrogen (for example tamoxifen), anti-prostaglandins and non-steroidal anti-inflammatory drugs is often started. A decrease or stabilization of disease is seen in 50 percent of patients. In a few cases a complete decrease of tumour growth was observed.

Hormonal Therapy

Tamoxifen is a selective oestrogen receptor modulator that is usually used in the treatment of breast cancer. As I mentioned before it is possible to use hormonal therapy for treatment of desmoid tumours. Prior to the start of treatment oestrogen- and/ or progesterone receptor positivity should be demonstrated in the tumour specimen. However, the exact mechanism for respone to tamoxifen is unclear since response to tamoxifen is not correlated to presence of estrogen receptor alpha alone. [1] Alternative pathways like insulin-like growth factor receptor or TGF ß might be involved.

Furthermore, desmoids tumours might respond to medroxyprogestrone acetate or in premenopausale women to the addition of LHRH-agonists to tamoxifen. [2]

Anti-Inflammatory Drugs

Because of the fact that desmoids might produce pro-inflammatory proteins, anti-inflammatory drugs can be given.
Most frequently sulindac is applied. Sulindac is a nonsteroidal anti-inflammatory drug and is able to reduce the growth of polyps and precancerous lesions in the colon, especially in association with familial adenomatous polyposis. Although sulindac and tamoxifen show response rates as high as 70 percent, [14] regression is usually partial.

Indomethacin is also used in the treatment of desmoid tumours. In a report published previously a complete resolution of a desmoid tumour being treated with indomethacin for 14 months was demonstrated. [15]
"In another patient, this drug caused an immediate response, then became ineffective. Treatment of a third case with indomethacin and ascorbic acid from the beginning produced shrinkage of the tumour which has continued to date." [16]
Nevertheless, indomethacin and ascorbic acid are associated with a high prevalence of gastro-intestinal side effects especially in long term use.
In recent years a new drug called celecoxib (celebrex) instead of sulindac has been applied due to its favourable gastrointestinal toxicity profile compared to unselective COX inhibitors. However, an essential point is that celecoxib can cause cardiovascular side effects and thus it should be considered since these drugs are administered over a long time period.

"NSAIDs still represent an attractive treatment option, particularly since they also influence the growth rate of polyps in patients with concomitant FAP or Gardener´s Syndrome and appear to protect against colon carcinoma."[1]

Chemotherapy

Even though desmoid tumours are histological benign fibrous neoplasm without metastatic potential, chemotherapy seems to have a good efficacy. Low dose of methotrexate and vinblastine "are well tolerated in children with desmoid-type

fibromatosis. Furthermore, this combination can promote tumour regression or block tumour growth in most children."[4]

Below the positive and negative effects of Methotrexate, Vinblastine, Doxorubicin, Dacarbazine and Carboplatin are mentioned:

- Methotrexate: Methotrexate is an anti-metabolite which inhibits the metabolism of folic acid.
  Precaution: Patients with psoriasis, rheumatoid arthritis, alcoholic or chronic liver disease, leucopenia or thrompocytopenia, and pregnant women should not receive Methotrexate.

- Vinblastine: Vinblastine is an antimitotic drug and is M-phase cell cycle specific.
  Precaution: Caution in patients who suffer from hematologic, dermatologic, gastrointestinal and neurologic symptoms.

- Doxorubicin: Doxorubicin inhibits topoisomerase II and leads to the destruction of DNA because it produces free radicals. Because of this fact it is able to inhibit the growth of neoplastic cells.
  Precaution: Myelosuppression and irreversible cardiac toxicity may arise. Caution in patients with impaired hepatic functions.

- Dacarbazine: Dacarbazine suppresses DNA, RNA, protein synthesis and cell replication during all phases of cell cycle.
  Precaution: Caution in patients who suffered from hepatic or renal insufficiency.

- Carboplatin: Carboplatin is an analogue of Cisplatin, but it is not so toxic.
  Precaution: It is very important to monitor the bone marrow function.

An additional problem is that radiation and chemotherapy may have side effects and can develop secondary malignant tumour.

Imatinib

In the following section a new therapeutic option with the tyrosine kinase inhibitor imatinib mesylate is described.
"An increasing number of reports suggest clinical and radiographic benefit from the tyrosine kinase inhibitor Imatinib (Glivec)."[1]
A tyrosine kinase is an enzyme that transfers a phosphate group from ATP to a tyrosine residue in a protein. Phosphorilation of protein by kinase is very important for signal transduction that regulates, for example growth, differentiation and apoptosis.

Imatinib mesylate shows inhibitory activity against tyrosine kinase including PDGFR α, PDGFR β and C-KIT subtype. However, recent evidence suggests that even patients with C-KIT negative tumours benefit from the therapy with inhibitors against the tyrosine kinase. Due to the fact that imatinib has only a few side effects, as for example emesis, nausea, diarrhoea, elevated liver enzymes and erythrodermia, it can be considered as a new treatment option for patients with aggressive fibromatosis.

High response rates were also achieved in therapy with gastrointestinal stromaltumours (GIST) by imatinib. Nevertheless, several reports described an imatinib resistance in GIST. "Although Imatinib has revolutionized the treatment of advanced GIST's, clinical resistance to this drug has proved to be a significant problem, with more prolonged follow-up."[17]

Furthermore, there might be other receptor tyrosine kinases which could be successfully blocked with imatinib. "One of them – macrophage-colony stimulating factor receptor (M-CSFR) – was established by the Australian investigators (Dewa et all. 2005)."[18]

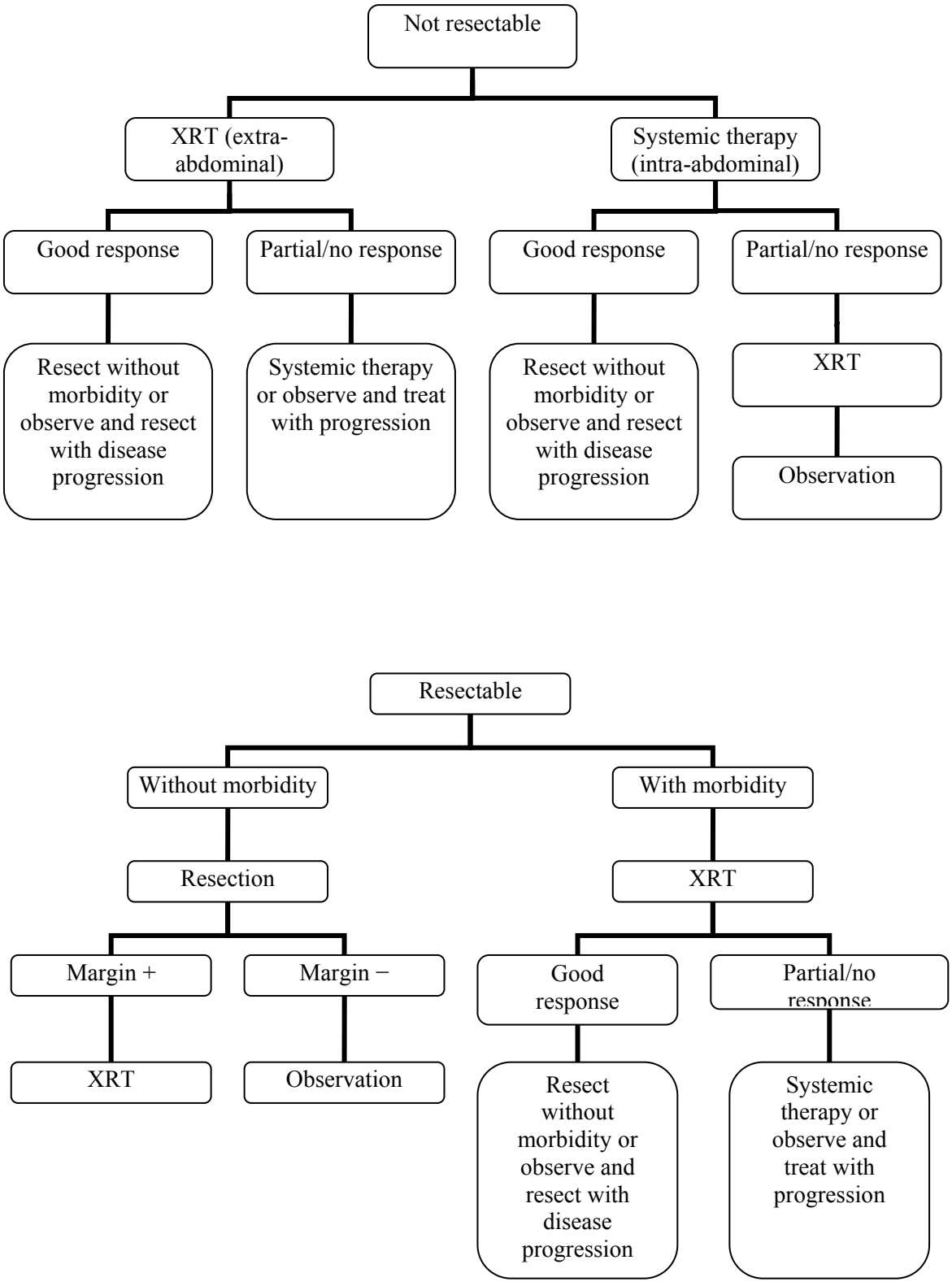


Figure 2: Optimizing Treatment of Desmoid Tumours [13]

5 Prognosis

The prognosis of desmoid tumours is ambiguous. In rare cases, the tumour stops to grow spontaneously and in many cases there is continuous tumour-growth. “Treatment recommendation should be based upon analysis of the risk-to–benefit ratio because of the inconsistent nature and response to treatment of this tumor.”[1]
If patients present with resectable tumours, surgery is the only choice.
Radiation therapy should be reserved to lesions which are unresectable or surgery would lead to functional or cosmetic defects.
For recurrent desmoids tumours the treatment of choice is again surgical resection and in case of positive margins a postoperative radiation therapy might result in better local control.
If tumours are judged to be unresectable, drug treatment with anti-hormonal strategies like tamoxifen, non-steroidal anti-inflammatory agents like sulindac, Cox-2 inhibitors like celecoxibe. or cytostatic treatment with doxorubicin or the combination chemotherapy with methotrexate plus vinblastine are possible treatment options. Very recently imatinib has been successfully employed in the treatment of unresectable desmoids tumours.
For patients with intraabdominal desmoids or Gardner’s Syndrome sulindac with or without tamoxifen should be used.

There exists no standard protocol for the follow-up of patients with this kind of tumour. However, typically patients are followed-up by clinical examination and radiographic studies every six months for the first two years, every 12 months to year six, and then biannually. [1]

The following case report demonstrates the successful treatment of a recurrent inoperable desmoids tumour developed in the pleura of the right lung with the tyrosine kinase inhibitor imatinib mesylate. In addition, long term remission after cessation of imatinib mesylate for more than 12 months was observed.

6 Case Report

Patient and Methods

A 36-year old male patient presented with pain and paresthesia in the right axilla in May 2002. A chest-X –ray was performed revealing a pleural mass (Figure 3). CT-guided biopsy of the lesion was carried out and histological work-up showed a diffuse increase of the connective tissue and a fibrous transformation of the musculature. Subsequent MRT-scans confirmed a large desmoid tumour of the right pleura cavity.

Complete resection of the tumour necessitated the excision of parts of the right thoracic wall and the fourth rib. The regular follow up examination were initiated and four months after surgery the patient complained about chest pain again. He described the same symptoms he experienced at the first presentation. Pain and paresthesia in the right thoracic wall led to the diagnosis of a recurrent desmoid tumour with compression of the right lung and plexus brachialis. The local recurrence was detected on magnetic resonance imaging (Figure 5) and CT scan and biopsies were taken. An immunohistochemical analysis was performed (Table 2). The immunohistochemistry showed that the tumour cells were positive for vimentin and desmin and showed focal positivity for SMA. No expression of CD34, S-100 and EMA could be demonstrated. The tumour stained negative for estrogen- and progesterone receptors but focal positivity for CD117 was noted (Figure 8).

Due to the fact that the tumour involved the plexus brachialis and radical surgical excision might have had led to a significant impairment of the function of the right arm the lesion was classified as inoperable. Therefore, medical treatment was initiated. Imatinib mesylate at a dose of 400mg per day was chosen on the basis of focal positivity of tumor for CD117 in addition to celecoxib 200mg twice a day to block Cox-2. During the first follow–up, stable disease was noted by MRI and the treatment was continued. In subsequent follow-up examinations necrotic areas with in the tumor were detected (Figure 6) and no further tumour growth was observed until September 2007. After an initial increase of pain within the tumour

which might have been treatment-associated which necessitated the initiation of analgesic treatment using opioids, pain diminished over time and analgesic treatment could be stopped permanently. After a response duration of three years COX-2 inhibitor-treatment was stopped and imatinib treatment was continued. The tumour size remained unchanged and the patient was free of symptoms. After more than 4 years of continuous stable disease imatinib treatment was abandoned in September 2007 as well. Despite the cessation of drug treatment no tumour progression was observed for more than 12 months now.

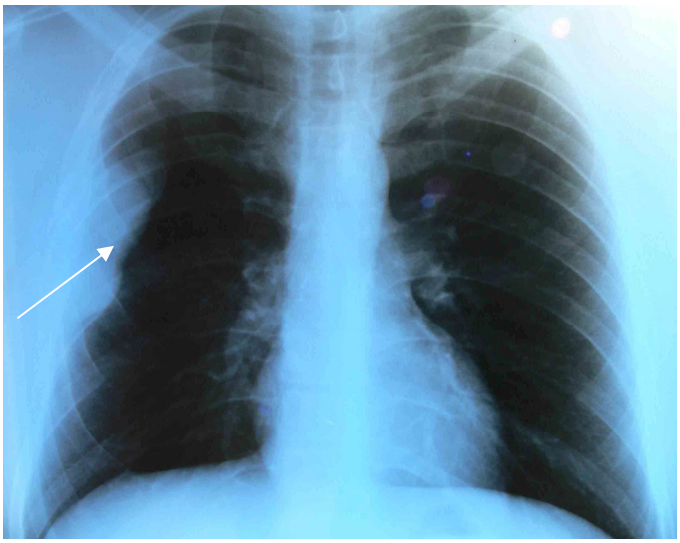


Figure 3: Chest X-ray of the thorax before surgical intervention (21.05.02) [19]

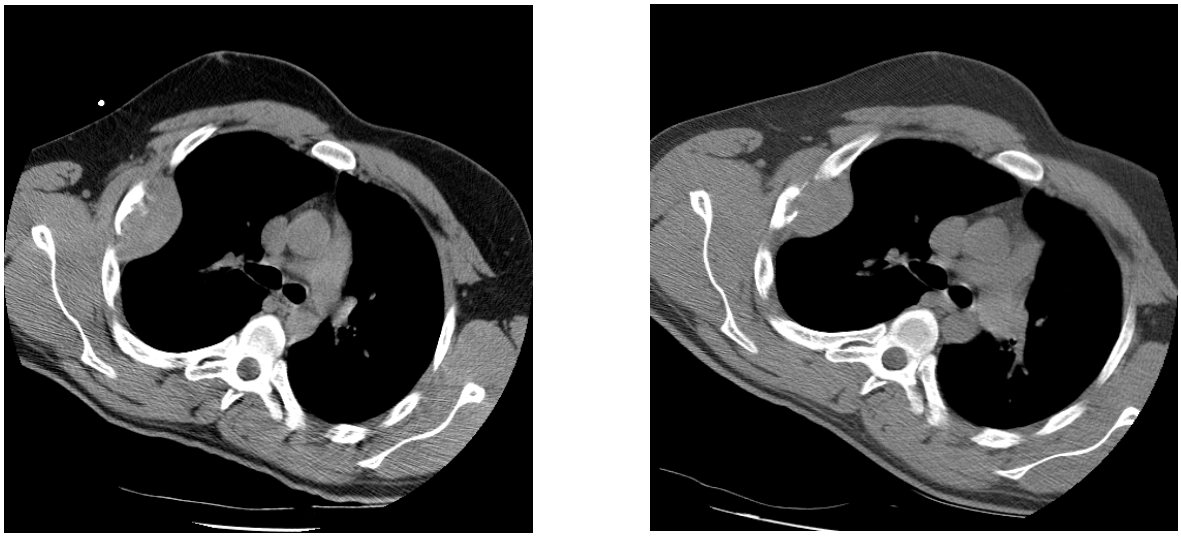


Figure 4: Computed tomography scans before surgical intervention
(left: 21.05.02; right 07.06.02)[19]

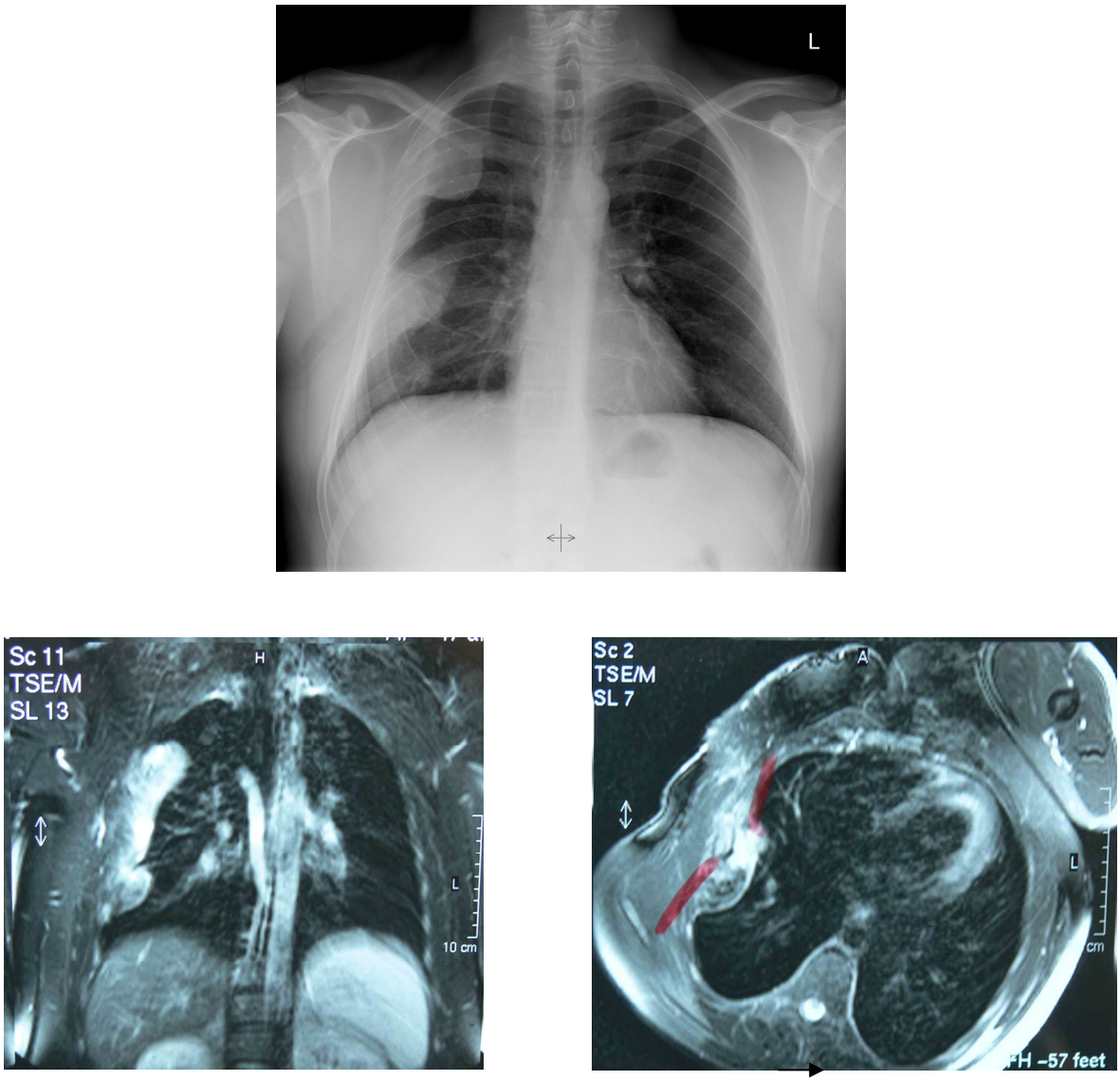
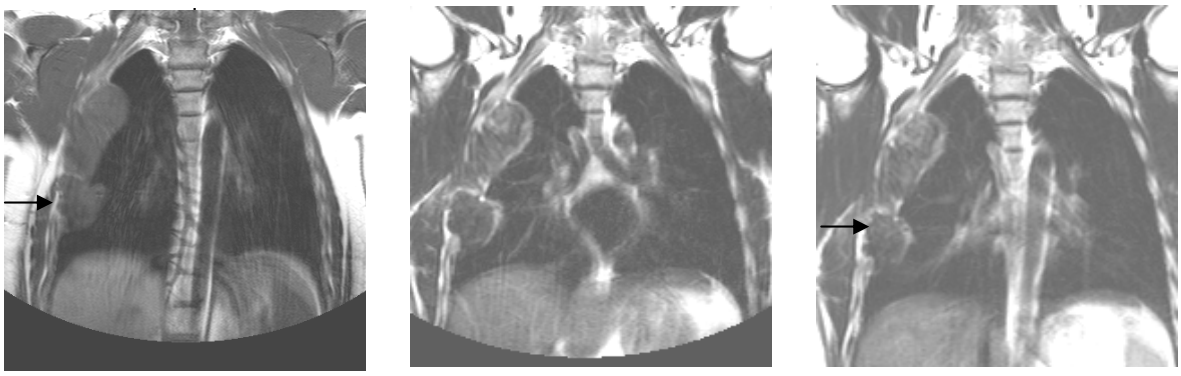


Figure 5: Chest X-ray and Magnetic resonance images showing a local recurrence (top: 16.01.2003; left: 14.02.2003; right 07.05.2003)[19]



A B C

Figure 6: Magnetic resonance images showing intralesional necrosis after therapy with imatinib mesylate. (A: 17.07.03; black arrow: solid lesion; B: 16.10.03; C: 21.01.04; Black arrow: cystic lesion indicating necrosis)[19]

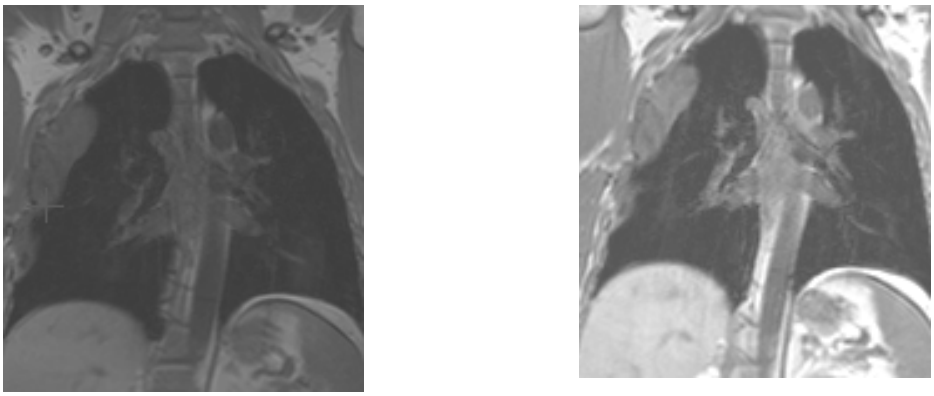
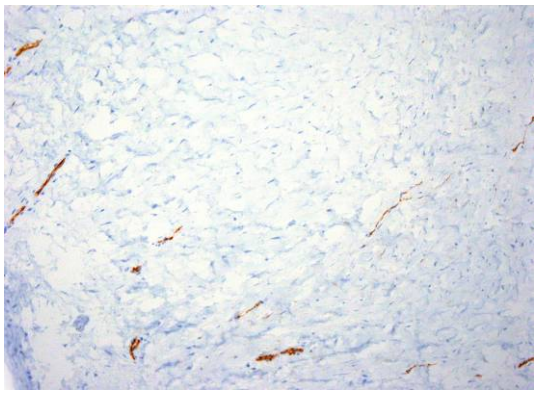
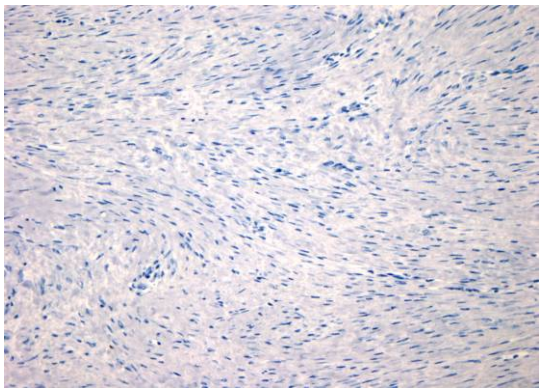


Figure 7: Growth arrest was observed lasting more than 4 years on treatment (left 31.08.07, right 29.01.2009)[19]

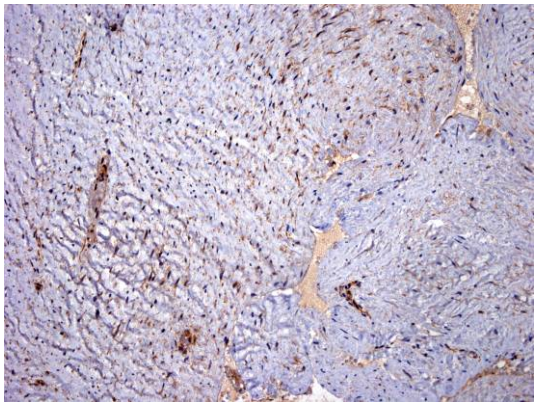
Immunohistochemical analysis:



a) magnification × 200



b) magnification × 200



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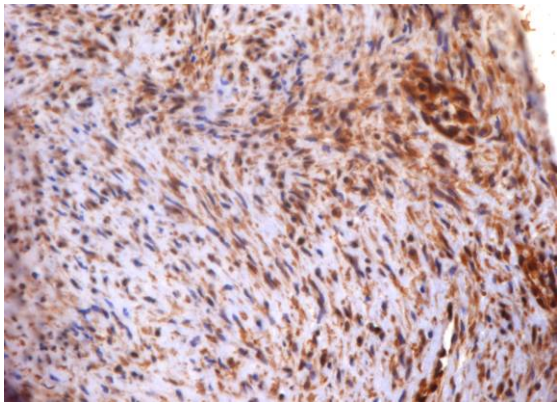
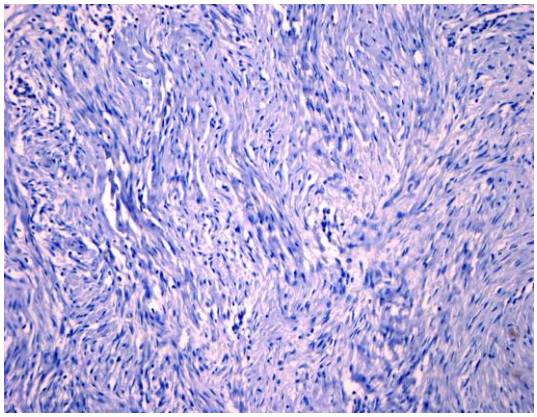
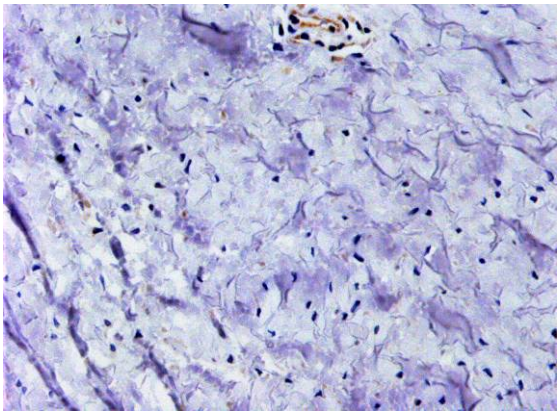


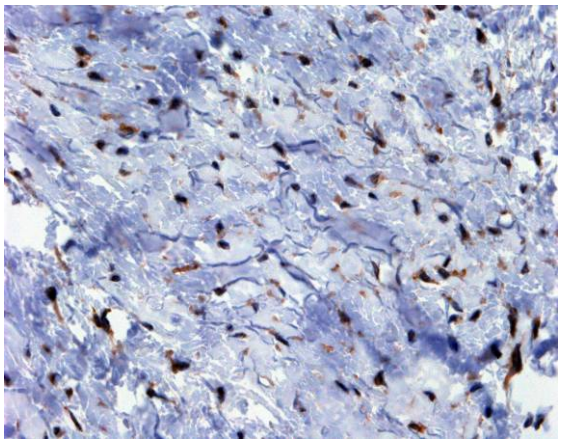
d) magnification × 400



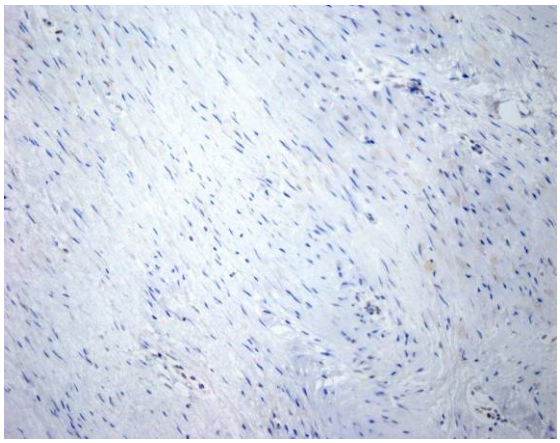
e) magnification × 200



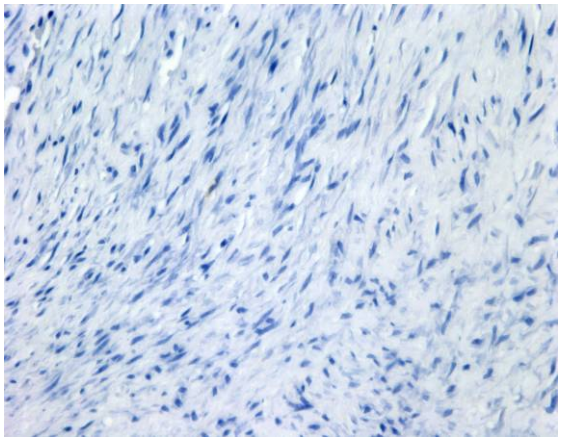
f) magnification × 600



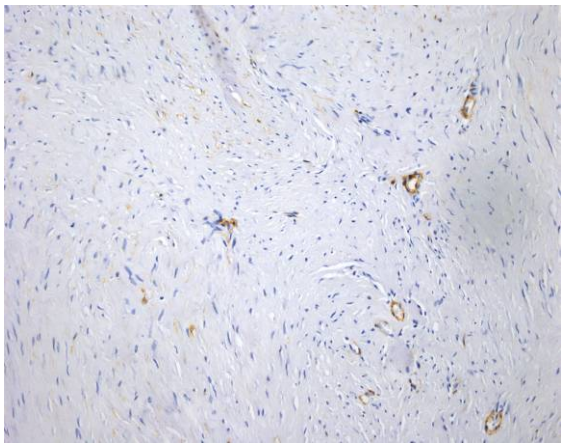
g) magnification × 600



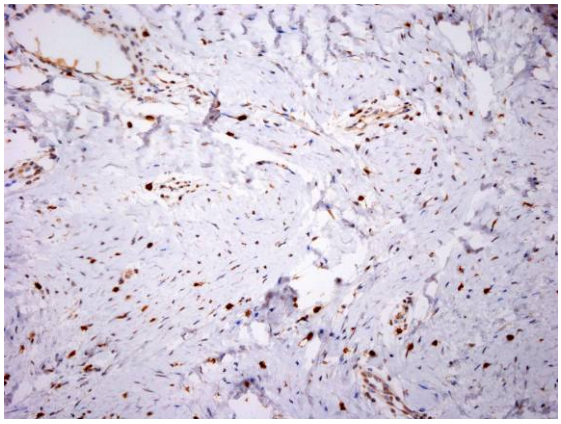
h) magnification × 200



i) magnification × 400



j) magnification × 200



k) magnification × 200

Figure 8: Immunohistochemical analysis showed that the tumour cells stained negative for CD34 **(a)**, COX-2 **(b)**, PDGF beta **(e)**, S-100 **(i)** and progesterone receptor **(h)**. They were generally positive for PDGF alpha **(d)**, PDGFR alpha **(f)**, PDGFR beta **(g)** and SMA **(j)**. In many cases, a positivity for IGFR **(c)** and a focally positivity of C-KIT (simulated by mast cells) **(k)** can be encountered. [20]

Table 2: Summary of antibodies and methods [20]

Antibody	Clone	Company	Dilution	Pretreatment	Detection system	Chromogen
ERα	1D5	Dako	r.t.u.	WB 40min	env+	AEC
PR	PgR636	Dako	r.t.u.	WB 40min	env+	AEC
CD31	JC/70A	Dako	1:50	CC1 mild	iView	AEC
CD34	QBEnd/10	NeoMarkers	1:800	CC1	iView	AEC
PDGFα	E10	Santa Cruz	1:1000	MW Dako 6,0	CM	AEC
PDGFRα		NeoMarkers	1:100	MW 9,0	env+	AEC
PDGFβ	H55	Santa Cruz	1:100	MW Dako 6,0	CM	AEC
PDGFRβ		NeoMarkers	1:100	MW 9,0	env+	AEC
COX-2	CX294	Dako	1:50	MW 9,0	CM	CM
IGFR		NeoMarkers	1:50	MW 9,0	CM	AEC
C-KIT	CD117	Dako	1:1000	MW 9,0	env+	DAB
S-100		Dako	1:2000	P2 12min	iView	DAB
SMA	1A4	Sigma	1:5000	CC1	iView	DAB

7 Results

Desmoid tumours remain a therapeutic challenge for oncologists, surgeons and radiotherapists. The main problem is that these tumours tend to have a high rate of relapse and in many cases the tumours grow slowly causing symptoms at a very late stage due to a big tumour mass involving vital structures.

In a retrospective analysis of the tumour of the patient using immunohistochemistry it could be shown that the tumour expressed PDGFR alpha and the tumour cells stained positive for vimentin, desmin and IGFR. In the original histology a low expression CD117 with a focal pattern was observed. The tumour cells were generally negative for CD34, S-100, progesterone and estrogen-receptors and COX- 2.

Earlier studies described that aggressive fibromatosis may express PDGFR alpha and beta as well as C-KIT. Our case demonstrated that aggressive fibromatosis might express PDGFR alpha as well. Originally, the decision to treat the patient with imatinib mesylate was based on the focal positivity of the tumour for C-KIT. However, in the retrospective re-evaluation of the tumour the focally positivity of C-KIT could be attributed to mast cells and not to the tumour cells. Nevertheless, the receptor tyrosine kinase of PDGF alpha is a target for imatinib mesylate and can be blocked using this drug.

After initiation of treatment with imatinib in combination with celecoxibe the rapid tumour growth was stopped. The patient was followed up by MRI every 3 to 6 months. At the 6^{th} months visit areas of necrosis within the tumour without further tumour progression was noted (Figure 6). Stable disease was observed throughout September 2006. Celecoxib treatment was terminated at this time point due to long lasting tumour response but imatinib mesylate treatment was continued. After a response duration of more than 4 years imatinib treatment was ceased and the patient was followed without any further drug treatment. Continued tumour response has been documented up to January 2009 (Figure 7).

The patient was meanwhile free of symptoms and is able to work during the whole time period of drug treatment. He has also raised a family and he is presently the

father of three healthy children. The conceptions of the children were observed during treatment with imatinib mesylate.

Taking everything into account it can be said that the therapy with imatinib mesylate seems to be an excellent treatment option for patients with inoperable desmoid tumours.

8 Discussion

Desmoid tumours are rare neoplasm and very difficult to manage in case of inoperable disease. An optimal treatment strategy is a challenge because of the fact that desmoids tend to have high rates of recurrence. There are many different drug treatment options but no standard drug treatment has been established.

Surgical resection is the primary therapy when medically and technically feasible. But as mentioned before desmoids tend to have high rates of relapses because of their infiltrative nature and possible multicentricity. Particularly wide local resection should be attempted. High risk of local recurrence in patients with positive or close resection margins was reported.[21,22,28,30] However, this finding is controversial since other reports have not found a correlation between the rate of local recurrence with negative or positive resection margins.[23,24,26,29] Nevertheless, the relationship between surgical resection margins and local recurrence is difficult to evaluate. “Most reports include only a small number of patients, group together intraabdominal and extraabdominal tumours as well as recurrent and primary disease, or include patients who have received multiple forms of treatment, including radiation therapy, surgery and chemotherapy.”[3]

The patient in the study suffered from a large desmoid tumour of the right pleura cavity. Initially, a resection of the tumour including parts of the thoracic wall and the fourth rib was performed. Four months later the patient complained about pain again and a local recurrence was noted on magnetic resonance imaging.

Due to the fact that the tumour involved the plexus brachialis and harboured the potential risk of a significant loss of the right arm’s function in case of surgical resection, the lesion was classified as inoperable necessitating other treatment options like radiation or drug treatment.

The role of the radiation therapy of recurrent inoperable desmoids tumours is controversial. Some reports demonstrated good local control of the tumour in patients who underwent radiation therapy [26-30]. Others could not find any benefits in using this kind of therapy [27,35,36].

Generally it can be said that radiation therapy may have a benefit when patients suffer from residual tumours with a diameter below 5 cm and in locations where a high radiation dose is applicable.

However, the patient described in this case report suffered from a large recurrent thoracic aggressive fibromatosis with compression of plexus brachialis and lung. Due to these factors radiation therapy was not feasible since radiation therapy in this special anatomical location would have been hampered by potential side effects affecting lung and neural structures.

Therefore, we decided to start drug treatment in this patient.

In the treatment of aggressive fibromatosis non-steroidal anti-inflammatory drugs have been widely administered. “In the literature, the overall response rate of NSAID therapy alone is approximately 50%. Responses to combinations of therapies, including anti-oestrogens, NSAIDs, vitamin K, warfarin, and vitamin C, have also been reported.”[3]

One new report describes cyclooxygenase-2 and plated-derived growth factor receptors as potential targets in the treatment of aggressive fibromatosis [25].

Signoroni et al demonstrated that aggressive fibromatosis is characterized by WNT/oncogene pathway alterations and this is leading to COX-2-mediated constitutive coactivation of PDGFR alpha and PDGFR beta. Therefore, these tumours might benefit from combined nonsteroidal anti- inflammatory drug and tyrosine kinase inhibitor treatment.

At the initiation of treatment in our case the expression of COX-2 in the tumour was not available and the decision to administer the Cox-2 inhibitor celebrex was based on case reports demonstrating activity of NSARs in aggressive fibromatosis. Although retrospective immunohistochemical analysis of COX-2 revealed that the tumour of our patient stained negative for COX-2, celecoxib might have been important for anti-tumour activity in combination with imatinib mesylate as mentioned above. Positive or negative staining of COX-2 may depend on the sensitivity and specificity of the various antibodies against COX-2 available. Furthermore, no standardized staining protocol for COX-2 exists up to now and a positive or negative result does not predict the potential effect of COX-2 inhibitor treatment.

Therapy with imatinib mesylate in addition to COX-2 inhibitor treatment was started based on the observation of focal positivity of C-KIT in the

immunohistochemistry and one report in the literature showing activity in this setting. [32]

“Imatinib mesylate is a selective inhibitor of certain tyrosine kinases including Abelson protooncogene (ABL), breakpoint cluster region (BCR)-ABL, Abelson–related gene (ARG), KIT (CD 117, stem cell factor receptor) and PDGFRs which is highly effective in the treatment of chronic myeloid leukaemia by inhibiting the kinase activity of the BCR–ABL fusion protein or dermatofibrosarcoma protuberans by inhibiting PDGFR activation related to the COL1/PDGF-beta fusion gene and in gastrointestinal stromal sarcomas (GIST) by inhibition of C-KIT or PDGFR.”[31] The authors of this study emphasized that if an activating mutation in a protooncogene cannot be found, it does not foreclose the effect of imatinib or other tyrosine kinases in patients with desmoid tumours.

“Mace et al. (2002) [32] used Imatinib mesylate in the treatment of two patients with advanced aggressive fibromatosis in a salvage setting. The patients had tumours which expressed C-KIT, PDGFR-alpha, PDGFR–beta at the level of either protein (detected by immunohistochemistry) or mRNA (detected by RT–PCR).”[18] To avoid amputation they were treated with imatinib. Both patients tolerated the therapy very well and they also showed a clinical response during the therapy.

Retrospective immunohistochemical analysis revealed that the tumour reported herein stained positive for PDGFR alpha. In the original histology a low expression CD117 with a focal pattern was observed. However, in the retrospective re-evaluation of the tumour the focally positivity of C-KIT could be attributed to mast cells and not to the tumour cells. Nevertheless, the receptor tyrosine kinase of PDGF alpha is a target for imatinib mesylate and can be blocked using this drug.

After initiation of treatment with imatinib in combination with celecoxibe the rapid tumour growth was stopped. At the 6th months visit areas of necrosis within the tumour without further tumour progression was noted. A long lasting tumour response for 3 years was observed. After this time period COX-2 inhibitor treatment was discontinued due to the fact that the patient did not experience any tumour related symptoms anymore and to avoid possible side effects. Sustained tumour control was demonstrated for another year with imatinib treatment alone. In September 2007 imatinib therapy was stopped and the patient was monitored closely by MRI examinations every 3 months thereafter. No tumour progression has occurred for more than one and a half year up to now.

Our case illustrates that a combination treatment with imatinib and COX-2 inhibitors might lead to a long lasting tumour response of desmoids. To our knowledge this is the first report that showed sustained tumour response after cessation of drug treatment for more than 18 months.
Our case is inline with previous reports that imatinib is a valuable drug to treat recurrent inoperable desmoids tumours.

At this point various clinical studies, in which patients were treated with imatinib mesylate, should be presented (Table 3):

Table 3: Use of Imatinib mesylate therapy for Desmoid Tumours in the Literature

Year	Reference	No. of patients	Drug	Response	Putative target
2002	Mace et al.[32]	2	Imatinib mesylate	2 CR	PDGFR alpha, PDGFR beta, KIT
2006	Heinrich et al. [33]	19	Imatinib mesylate	3 PR, 4 SD	PDGFR beta
2006	Folla et al. [34]	1	Imatinib mesylate	1 PR	PDGF, IL-6, tumour necrosis factor alpha, insuline
2007	Seinfeld et al. [37]	1	Imatinib mesylate	1 PR	KIT
2007	Wcislo et al. [18]	1	Imatinib mesylate	1 CR	KIT, PDGFR beta
2007	Ioannov et al. [38]	14	Imatinib mesylate	0	KIT
2008	Ezumi et al.[39]	1	Imatinib mesylate, NSAID, Tamoxifen. HMGCoA reductase inhibitor	0	KIT
2008	Heinrich et al. [40]	20	Imatinib mesylate	0 CR, 2 PR, 8 SD, 7 PD, 3 unknown	PDGFR alpha
Total		59		3 CR, 7 PR, 12 SD, 7 PD, 3 unknown	

CR, complete response; PR, partial response; SD, stable disease, PD, progressive disease

An alternative to NSARs and imatinib hormonal therapy could be used for the treatment of these tumours. However, the desmoids tumour should express hormone receptors either oestrogen or progesterone receptors to be a candidate for this treatment strategy. The tumour of our patient was negative for both hormone receptors. Consequently, no anti-hormonal treatment was initiated. Nevertheless, there is a higher incidence of desmoid tumours, especially in the abdominal wall, during or soon after pregnancy or while taking oral contraceptives illustrating the potential role of sex hormones in the pathogenesis of these tumours. There have also been reports of spontaneous regression of desmoids after menopause and after oophorectomy."[3] Furthermore, evidence exists that desmoid tumours might be responsive to endocrine treatment with goserelin acetate plus tamoxifen in premenopausal women or with tamoxifen as a single agent independent of sex and age. [2]

Low dose chemotherapies using doxorubicin, vinblastine and methotrexate have been employed in the treatment of desmoids tumours not responding to the above mentioned treatment options. "Doxorubicin based-combination regimes are reserved for refractory cases, patients with rapidly growing tumours, or those who are highly symptomatic."[6]

Since our patient responded well to first-line combination therapy with imatinib mesylate and a COX-2 inhibitor, chemotherapy was not considered. In any case it is very important to balance risk and benefit of planned treatment without compromising the patient's quality of life.

9 Conclusion

This case demonstrated that aggressive fibromatosis might express PDGFR alpha and treatment with imatinib mesylate may lead to long lasting favourable response of these tumours. The combination of imatinib mesylate with COX-2 inhibitors, such as celecoxib seems to be attractive, on the one hand, to alleviate symptoms such as pain and, on the other hand, to potentiated anti-tumour activity. Even in tumours staining negative for COX-2 treatment response might be seen since the available COX-2 antibodies vary in both sensitivity and specificity and no standardized protocols for COX-2 detection is available.

The combination treatment is well tolerated over a long period of time.

This is the first report demonstrating that long lasting sustained continuous response of a desmoid tumour might be observed after cessation of drug treatment with imatinib. A possible consequence of our finding might be that imatinib treatment might be stopped after reaching best tumour response in patient with inoperable desmoids tumours. Using this new treatment strategy would help avoiding potential side effects of imatinib and would save treatment costs since imatinib is a very expensive drug.

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Curriculum vitae

Persönliche Daten :

Daniela Hetzel
Lindengasse 1
8045 Graz Andritz
Tel: 0650/6801117
e-mail: daniela.hetzel@stud.medunigraz.at

geboren am: 27.09.1983
Religion: röm.kath.

Schulausbildung :

09/1994 – 06/2002 :	Bundesrealgymnasium Knittelfeld
25.06.2002 :	Reifeprüfung abgelegt

Hochschulausbildung :

10/2002 :	Beginn des Medizinstudiums an der Medizinischen Universität Graz
04/2004 :	Famulatur in Neurologie am LKH Judenburg-Knittelfeld bei Prim. Univ.- Doz. Dr.Offenbacher (2 Wochen)
09/2005 :	Famulatur in Innerer Medizin am LKH Judenburg- Knittelfeld bei Prim.Dr.Rainer (2 Wochen)

02/2006 : Famulatur in Innerer Medizin am
LKH Judenburg- Knittelfeld
bei Prim.Dr.Rainer (2 Wochen)

09/2006 : Famulatur in Unfallchirurgie am LKH Judenburg-Knittelfeld
bei Prim. Univ. Doz. Seitz (4 Wochen)

02/2007 : Famulatur in Gynäkologie und Geburtshilfe am
LKH Judenburg-Knittelfeld bei Prim.Dr.Klug (2 Wochen)

09/2007 : Auslandsfamulatur in Anästhesie an der
University of Medicine and Pharmacy in
Ho Chi Minh City / Saigon, Vietnam (4 Wochen)

Begleitende Tätigkeiten :

2005 – heute : Ehrenamtliche Tätigkeiten beim
Österreichischem Roten Kreuz in Knittelfeld

Persönliche Interessen :

Bergwandern, Schifahren, Lesen

Besondere Kenntnisse :

Sprachen : Englisch (fließend)
Spanisch (Grundkenntnisse)

EDV Kenntnisse in Office