Journal of BUON **15:** 188-195, 2010

LETTERS TO THE EDITOR

Good clinical practice in chronic myeloid leukemia: advances and prospects at the Institute of Oncology of Moldova

Dear Editor,

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder resulting from the stem cell neoplastic transformation caused by translocation between the long arms of chromosomes 9 and 22. The annual incidence of CML ranges between 0.8-1.6 cases per 100,000 population [1,2] and accounts for 15% of leukemias in adults [1]. The clinical course of the disease comprises 3 consecutive phases: chronic, accelerated, and blast crisis and may be associated with life-threatening emergencies [1-3]. Conventional treatment of CML includes chemotherapy, interferon-α, bone marrow (BM) transplantation [1-4]. Conventional chemotherapy (CChT) doesn't reduce significantly Philadelphia (Ph) chromosome-positive cells. CML therapy has dramatically changed with the advent of the small molecule tyrosine kinase inhibitor – imatinib mesylate (Glivec®) [1,4,5] which blocks the production of the abnormal protein BCR-ABL, that causes the irregular proliferation of myeloid cells. Glivec® International Patient Assistance Program (GIPAP) is one of the most generous, far-reaching assistance programs ever developed for cancer therapy, aiming at providing imatinib for patients with certain malignant neoplasias. Imatinib mesylate has demonstrated significant activity in patients with all phases of CML, whether they received prior therapy or not, leading to the highest clinico-hematological, cytogenetic and molecular response in chronic phase [1-3,5].

In this communication we aimed to evaluate the diagnosis assertion, the management options, the short-term results and the safety of imatinib therapy in patients with different phases of CML in Moldova. We studied 43 Ph-positive CML patients (22 males and 21 females) aged 15-61 years, treated with imatinib mesylate and followed-up between 2006-2008 at the Department of Hematology of the Institute of Oncology, Chisinau, Moldova. All of them were approved for GIPAP. Novartis Pharma AG is the donor organization and the manufacturer of Glivec®, supporting GIPAP by providing Glivec® to Ph-positive CML patients. The period between diagnosis to starting imatinib ranged from 1 to 59 months (median 24.7). Leukocyte count ranged between 12.2–315.0 × 10^9/l, and platelet count 180–2340 × 10^9/l. Granulocytes' lineage in the BM aspirates varied between 34 and 86.4%. BM blast cells range was 1-69%. Complete hematological response (CHR) was obtained in 39 (90.6%) patients within 1-2 months of the imatinib therapy and proved superior ($p < 0.05$) to that achieved with CChT and interferon-α. A trend to earlier CHR was observed in cases with chronic phase, shorter duration of CML, and lower leukocyte and platelet counts. The follow-up cytogenetic analysis of the BM revealed decrease of Ph-positive cells up to 20-33%. In 3 (6.9%) patients complete cytogenetic response was obtained. Patients primarily treated with imatinib did not develop hematological emergencies and severe hematological toxicity compared with those treated with CChT.

The combined screening for Ph chromosome and BCR-ABL p210 oncogene is highly useful for confirming the diagnosis in patients suspected for CML. Imatinib mesylate currently remains an effective and quite tolerable first-line targeted treatment in chronic and accelerated CML phases, even in cases initially managed with CChT and interferon-α. Response to imatinib correlates with individual characteristics of CML. The earliest CHR may be achieved in cases with chronic phase, shorter duration of CML, and lower leukocyte and platelet counts. GIPAP improved the standards of diagnosis and treatment of CML in Moldova. Imatinib-refractory patients should be considered for second-line treatment with nilotinib within the framework of Tasigna® International Patient Assistance Program.

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Rare site of metastasis of non-small-cell lung cancer

Dear Editor,

A 35-year-old male, a plumber by occupation, presented with superior vena cava syndrome in July 1999. A diagnosis of stage IIIa adenocarcinoma of low differentiation (upper lobe mass in the right lung and mediastinal lymph node enlargement) was determined. Bronchoscopy showed tumor involvement of the main right bronchus < 2 cm from the carina bifurcation.

The patient underwent 6 courses of chemotherapy with cis-platinum (100 mg/m^2) and paclitaxel (175 mg/m^2) and achieved good partial remission. Bronchoscopy after treatment indicated residual disease at the main bronchus and radiotherapy (50 Gy) was applied. A computed tomography (CT) scan showed complete remission.

The patient returned to work 4 months after the discontinuation of treatment. Swelling of the right thumb gradually developed. X-rays of the hand revealed that half of the last phalanx bone was missing (Figure 1). The patient was right-handed and his occupation had involved extensive use of the right thumb. CT scans of the abdomen and chest showed no recurrence. A bone scan (Figure 2) revealed only a positive spot on the right thumb. The right thumb was surgically amputated. Histology was the same as that of the lung.

Lung cancer often metastasizes to other organs and metastatic disease is detected at diagnosis in approximately 50% of cases [1]. Patients at stage IIIa and IIIb disease may present with metastases after the diagnosis and treatment failure. The sites of single metastases are in the liver (11.22%), skeleton (21.42%), brain (9.69%), adrenals (7.65%), the other lung (10.20%) and in multiple organ sites (39.79%). Skeletal metastases are located mainly in the spine and/or pelvic bones and the large majority affect multiple foci of the skeleton. Metastases rarely affect the limbs [2,3]. The above data originate from a study of 372 patients. Fifty-two patients in another trial showed skeletal metastases in 4.9% of the patients, and 32.3% in the liver, 6.5% in the adrenals, 12.9% in the other lung, and 3.2% in the

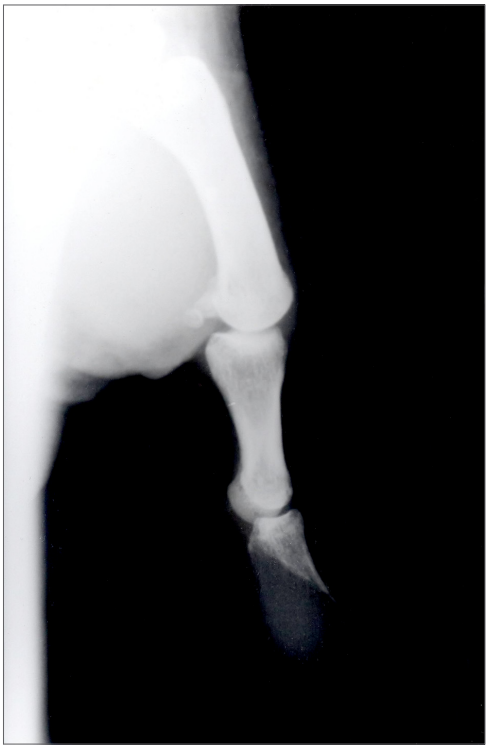

Figure 1. X-rays of the right hand. Half phalanx is missing.

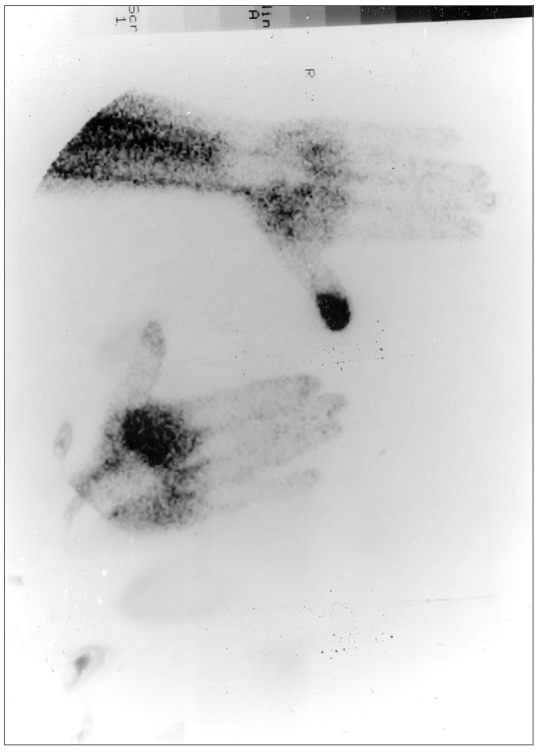

Figure 2. Bone scan. Positive spot only on the right thumb.

brain. Single metastasis in the limbs without any other metastatic disease has not been described in the literature, particularly while the lung disease was in complete clinical and laboratory remission [4,5].

There is no way to interpret and justify the metastasis in the right thumb of the patient described in this report. Multiple usage of his right hand and specifically his right thumb as a plumber, may have produced, over time, as in Latin, "locus minoris resistentiae" (location of low resistance). We report this case in view of the rare metastatic site.

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Neuroendocrine carcinoma presenting as jaundice in a patient with von Recklinghausen's disease

Dear Editor,

Von Recklinghausen's disease (VRD), also known as neurofibromatosis type 1, is an autosomal dominant disorder clinically associated with a variety of neuroendocrine tumors (NETs) [1]. In the last 20 years pancreatic NETs have been recognized with increased incidence in patients with VRD.

Herein, we report on a 71-year-old woman with VRD admitted to our Department with a presumptive diagnosis of pancreatic tumor affecting the second portion of the duodenum.

Her health problem had started 3 months ago with painless jaundice. Upper gastrointestinal tract endoscopy showed multiple polypoid lesions in the bulbus, histologically diagnosed as inflammatory lesions. She had a daughter with history of neurofibromatosis.

The patient's VRD was described as multiple café-

au-lait spots and generalized cutaneous neurofibromas in the trunk, confirmed by skin biopsy. While jaundice and abdominal pain were her main symptoms, no manifestations of functioning NET were found. Ophthalmological examination was negative for Lisch's nodules. Common tumor markers (CEA, CA 19.9, CA125, AFP) as well as laboratory routine tests were within normal range except increased liver function tests. An abdominal CT scan and MRI showed a 5×3 cm mass extending from the head of pancreas to the second portion of the duodenum. The characteristics of NETs on MRI are not different from an adenocarcinoma of the pancreas with hypointense to the pancreas on T_1-weighted images and isointense to the pancreas on T_2-weighted images, as in our case. MRCP additionally revealed intrahepatic bile duct dilation and compression of the common bile duct by the external mass. Indium-111 octreotide scan demonstrated normal uptake.

At laparotomy, the head of the pancreas was grossly enlarged and a tumor mass (5×4 cm) encased the portal vein, and extended to involve the duodenum. Multiple tumor lesions were identified on the jejunal wall, histologically diagnosed as reactive lymph nodes on frozen section. Frozen sections of the pancreatic tumor and peripancreatic lymph nodes were positive for adenocarcinoma. A hepaticojejunostomy with an end-to-side anastomosis of the hepatic duct to a Roux-en-Y limb of jejunum and biopsy of jejunal lesions were performed. The final histological examination of the specimens established the diagnosis of a NET with strong immunohistochemical expression (synaptophysin, NSE, chromogranin and EMA were positive, and CK7, CK19 and CK20 were negative) associated with nodal metastases. The postoperative course was uneventful.

In some reports, VRD was found with different NET types such as somatostinomas, PPoma and non-neurogenic malignancies such as GISTs [2,3]. In most cases diagnosis is often delayed, which may lead to a clinical and pathological diagnosis made after surgery with invasion of the adjacent organs and metastases to the lymph nodes. NETs are characterized by tumor size > 2 cm, invasion into adjacent tissues, angioinvasion and invasion into perineural spaces and the presence of synaptophysin, NSE, PGP 9.5, and chromogranin, with > 2 mitoses per 10 high-power fields. In our case, NET was suspected by the presence of lymph node metastases, tumor size and overexpression of synaptophysin, NSE, chromogranin and EMA.

The symptomatic conditions created by oversecretion of hormones (gastrin, secretin, glucagon) may be treated with H2-blockers, omeprazole and somatostatin and its long-acting analogs. A curative surgery with a pancreaticoduodenectomy is the treatment of localized and functionally inactive NETs, while chemotherapy is often used in metastatic NETs [4,5]. With today's radiographic methods and even via direct macroscopic inspection of the pancreas during the operation it is difficult to diagnose NETs in patients with VRD. In conclusion, a high degree for suspicion of pancreatic NET should be raised in patients with VRD developing jaundice.

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Synovial sarcoma of the thigh mimicking chronic cystic hematoma: a rare manifestation

Dear Editor,

Synovial cell sarcoma is an uncommon neoplasm affecting mostly the distal extremities. The tumor may be biphasic on histology, or rarely monophasic with only spindle cells. Cystic areas seen clinically may be due to a vascular hemangiopericytoma-like architecture, with tumor hemorrhage [1]. However, a purely cystic presentation over a prolonged period is very rare in sarcomas, especially in synovial sarcoma [2-4]. We treated a patient with a proximal thigh synovial cell sarcoma masquerading as a chronic cystic hematoma.

A 23-year-old woman presented with one-year history of a progressive mildly painful swelling over the medial upper left thigh, following trivial trauma. There were no neuromuscular symptoms. On examination, there was a 10×10 cm, non-tender, soft, fluctuant swelling with no skin changes. Radiographs of the adjacent joints were normal. Suspecting hematoma or bursitis, aspiration of 200 mL of serosanguinous fluid was done to evacuate the swelling. The coagulation profile and cyst fluid biochemistry were unremarkable. After 6 months, there was recurrence at the same site. Repeat coagulogram was normal. Ultrasonography was suggestive of a chronic hematoma. Excision was planned, and we found a large hematoma with ill-defined walls in the intermuscular spaces. Evacuation was performed, and wall biopsy was normal. Another recurrence a year later which was larger (15×12 cm), tender, lobulated, and with variable consistency, prompted an MRI scan which revealed a large heterogeneous lobulated soft tissue density mass in the thigh adductors with hemorrhage, suggestive of rhabdomyosarcoma or leiomyosarcoma. The surrounding planes were normal. Wide local excision was performed with primary closure. Histopathological examination revealed biphasic areas of spindle cells in fascicles, and polygonal epithelial cells in diffuse sheets, indicative of synovial sarcoma. All margins were uninvolved. After adjuvant chemoradiation, the patient was well one year later with normal follow-up MRI scans.

Despite the varied clinical presentations and diverse histology of sarcomas, it is rare for synovial sarcoma to present as a purely cystic lesion of prolonged duration. An electronic search on Google and PubMed using MeSH keywords "sarcoma", "hematoma", "cystic", and "mimicking", located only 2 such articles. Mann et al. [3] reported a 36-year-old man who presented with a suspected hemophilic pseudotumor in the thigh. Failure of repeated MRI imaging and therapeutic aspiration prompted an open biopsy 6 weeks later, which revealed synovial sarcoma. Engel et al. [4] operated a young man with a history of trauma to the thigh, with subsequent suspected organizing hematoma. Postoperative histopathology revealed synovial sarcoma. In a retrospective analysis of 31 patients of soft tissue malignancies with diagnostic delays (mean 6.7 months), Ward and colleagues [2] concluded that absence of ecchymosis in a chronic hematoma is suspicious of a neoplasm, as even CT and MRI findings may be equivocal. Aggressive open biopsy would be justified in these patients.

Some authors have also reported chronic hematomas mimicking soft tissue neoplasms [5]. In our case, the most unusual feature was the marked cystic consistency of the lesion. During the first biopsy, no gross solid tumor tissue was identified. However, incisional biopsy is usually helpful in diagnosis [2-4]. MRI is universally considered the most useful imaging technique for soft tissue lesions, but may be inconclusive in some situations [2,3]. This is because the MRI signal intensities identify physicochemical properties, and hence, gross morphology of the lesion, rather than the histology. Also, time-dependent changes, like necrosis and hemorrhage, can occur, making differentiation from benign lesions difficult [5].

Our case underscores the fact that in a slowly growing but non-resolving soft tissue lesion, clinical suspicion of malignancy should be high. MRI may be helpful in diagnosis. An adequate open biopsy should be undertaken early in these patients.

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Lung cancer presenting with extreme leukocytosis

Dear Editor,

Leukemoid reaction (LR) is common during the course of gastrointestinal, genitourinary, head and neck, and lung cancers [1]. Although the underlying cause of LR is still unclear, increased cytokine production is most widely accepted. Particularly increased granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) production induced by IL-1, IL-3 and IL-6 is considered to be responsible. LR is a late phenomenon in malignancies; it usually occurs just before death. It is more common in metastatic disease and is correlated with short survival [2]. This process is characterized by the release of mature neutrophils and band forms from the bone marrow storage pool [3,4]. We describe here a patient with non-small cell lung cancer (NSCLC) presenting with extreme leukocytosis.

A 45-year-old male presented to the emergency room with malaise, fatigue and high grade fever which had started one week ago. Physical examination was normal except a submandibular lymph node of 1 cm diameter. Laboratory examinations revealed white blood cell count (WBC) 53,000/μL, normochromic normocytic erythrocytes, hemoglobin (Hb) 12.9 g/dL, and platelets 422,000/mm^3 with an erythrocyte sedimentation rate of 91 mm/h. Leukocyte alkaline phosphatase (LAP) activity was 45 (range 40-150). Bone marrow biopsy revealed an increase in the granulocyte lineage without basophilia and eosinophilia, not consistent with chronic myeloid leukaemia (CML).

Hybridization with single bcr-abl fusion was detected in 7% of 200 interphase nuclei in bone marrow FISH analysis. Chromosome analysis was performed due to the 10% false positivity of the FISH analysis and t (9:22) anomaly was not documented. Thoracic and abdominal CT scans revealed a 15 mm mass in the upper lobe of the right lung and bilateral lesions in the adrenals, suggesting metastases. Biopsy from the adrenals revealed NSCLC and treatment was initiated accordingly. After exclusion of other possible causes of LR, this was attributed to paraneoplastic syndrome due to NSCLC.

The incidence and course of LR in cancer patients is not well established and the knowledge on this is based on case reports. Serum G-CSF levels are increased, particularly in squamous-cell lung, ovarian and urothelial cancers and tend to decrease with treatment [3]. LR in advanced-stage malignancies are usually myelocytic with accompanying eosinophilia, basophilia and monocytosis; blasts or nucleated red cells are not present.

The lack of thrombocytopenia and increased LAP score is critical in the differentiation of LR from CML. The close-to-normal LAP score and the lack of thrombocytopenia do not suggest CML as our patient [5] who had presented to the emergency room with leukocytosis and was firstly investigated for an infectious disease. After exclusion of an infectious cause, he was referred to our clinic with a presumptive diagnosis of leukemia. The examinations revealed paraneoplastic syndrome due to metastatic NSCLC and appropriate treatment was initiated.

This report constitutes the unusual case of LR associated with NSCLC in the literature. In patients with extreme leukocytosis, paraneoplastic LR associated with malignancy should be considered in the differential diagnosis of extreme leukocytosis.

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Squamous cell carcinoma of the lung with anal canal metastasis

Dear Editor,

Gastrointestinal metastases from primary lung carcinoma are very uncommon and anal canal metastases are extremely rare. A 64-year-old man presented with a mass about 1.2 cm in diameter involving the upper lobe of the left lung with bulky mediastinal lymphadenopathy and pleural effusion. Histologic examination of mediastinal lymph nodes and pleural effusion specimens demonstrated poorly differentiated squamous cell carcinoma. No distant metastasis was detected. Stage IIIB non-small cell lung carcinoma with malignant pleural effusion was diagnosed and the patient started combination chemotherapy with cisplatin and docetaxel. Four months after the 4th chemotherapy course he presented with gluteal pain and rectal bleeding. On rectal examination, a polypoid mass 1 cm in diameter was palpated. Pelvic MRI demonstrated a protruding lesion in the anal canal. Excisional biopsy was performed and histopathological study revealed poorly differentiated squamous cell carcinoma consisting of discohesive and pleomorphic cells with the same morphology of the primary lung cancer. This was considered to be a metastasis of squamous cell lung carcinoma, therefore palliative radiotherapy was delivered with complete gluteal pain relief and stoppage of rectal bleeding.

Although the frequency of gastrointestinal metastases of primary lung carcinoma is not exactly known, it is reported to range between 4.7-14% in autopsy series. In contrast, symptomatic gastrointestinal metastases are seen in only 1.77% of the patients [1]. Large cell carcinoma and adenocarcinoma are the most common types of lung cancer metastasing to the gastrointestinal system. Frequently, gastrointestinal metastases occur in the oesophagus, stomach and small intestine. Less frequently are seen in the colon and rectum, while they are only rarely seen in the anal region [1]. In the literature 4 cases of anal metastasis from lung cancer are reported; two of them were squamous cell carcinoma [2,3], one adenocarcinoma [4] and the fourth anaplastic cell carcinoma [5].

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Pulmonary Langerhans cell histiocytosis in a patient previously treated for germ cell tumor

Dear Editor,

Pulmonary Langerhans cell histiocytosis (PLCH), also known as pulmonary histiocytosis X or eosinophilic granuloma, is an uncommon interstitial lung disease in young adults [1,2]. It consists part of a spectrum of disorders called Langerhans cells histiocytoses (LCH), which are characterized by proliferation and infiltration of various organs by Langerhans cells. Association of PLCH with a malignant neoplasm is rare [3]. We report the first to our knowledge occurrence of PLCH in a patient with a history of metastatic germ cell tumor.

A 31-year-old man visited our hospital complaining of chest pain and dyspnea on exertion of a few days

duration. The patient's oncological history started 4 years earlier when a left testicular embryonal carcinoma with multiple pulmonary bilateral metastases was diagnosed. Left orhiectomy was followed by 4 cycles of bleomycin, etoposide and cisplatin chemotherapy with complete disease remission. He then remained on regular outpatient follow up. Based on the aforementioned patient's oncological history we proceeded to further examinations. All blood tests were normal. The chest CT showed bilateral intrapulmonary "ring-shaped" structures and nodular lesions in the upper lobes. A positron emission tomographic (PET) scan was done, without abnormal uptake by the nodules. A diagnostic segmentectomy was performed and the immunohistochemistry showed the presence of Langerhans cells (S100 and CD1a positive). At one-year follow up and after smoking cessation, the patient was asymptomatic and the chest CT revealed only one 8 mm nodular lesion in the left upper lung lobe, which remained stable in subsequent evaluation.

Although in the vast majority of patients with multiple lung nodules and relevant medical history recurrence of disease is the working diagnosis, other conditions should always be considered, including infectious (fungal, mycobacterial and septic emboli), inflammatory (Wegener's granulomatosis, rheumatoid nodules, sarcoidosis, LCH), and congenital (arteriovenous malformations).

PLCH is an interstitial lung disease of unknown etiology. The only consistent epidemiologic association is with cigarette smoking. Patients usually present with cough and dyspnea, but symptoms may be minimal or absent [1]. Chest radiograph is abnormal in most patients with micronodular or reticulonodular lung's appearance. An essential part of treatment is smoking cessation. Corticosteroids are the mainstay of medical therapy but chemotherapeutic agents such as vinblastine, methotrexate, cyclophosphamide, etoposide, and cladribine are also used in patients with progressive disease [2].

The pathogenesis of LCH is still an unsettled issue. It is unclear whether LCH is a reactive disease (due to an external trigger of proliferation) or a neoplastic process (due to an intrinsic autonomous proliferation) [4]. Egeler et al. hypothesize that LCH might be caused by the combination of oncogenesis and chronic immune dysregulation [5].

Association of PLCH with a malignant neoplasm is rare [3]. In most cases PLCH occurs in patients with haematological malignancies (lymphomas and leukemias), and only rarely in patients with solid tumors (particularly lung cancer). Neoplasms can precede, occur concurrently or follow the development of the disease. Egeler et al. [3] reported that in cases where malignancy precedes PLCH, the Langerhans disease could be a histiocyte reaction to the primary neoplasm, whereas when malignancy follows or coexists with PLCH, the neoplasm may be related to the therapy against PLCH. Furthermore, the development of lung carcinoma and PLCH in the same patient may be explained partly by the association of both conditions with cigarette smoking.

Our literature review revealed that cases with both PLCH and cancer do exist; still, whether there is a true association between the two diseases, is not clear so far. Thus it is always prudent to maintain clinical suspicion of potential malignancies in patients with PLCH.

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