

LETTERS TO THE EDITOR

Non-alcoholic fatty liver disease, metabolic syndrome and gastric cancer: Single center experience

Dear Editor,

Metabolic syndrome is a constellation of interrelated risk factors including high blood pressure, increased waist circumference, high triglyceride, low high-density lipoprotein and impaired glucose metabolism [1]. Recent data shows strong evidence for metabolic syndrome which confers an increased likelihood of colorectal cancer in addition to atherosclerotic cardiovascular diseases [2]. Non-alcoholic fatty liver disease (NAFLD) as a hepatic manifestation of metabolic syndrome, is defined by the presence of macrovesicular fat in more than 5% of hepatocytes, in the absence of significant alcohol use or other secondary causes of steatosis [1]. High prevalence of NAFLD, especially in Western countries (20-46%), makes it an obviously important issue of concern [2]. Insulin resistance plays a key role in colorectal carcinogenesis in patients with NAFLD [3]. Adiponectin is an adipokine that is found in decreased concentrations in those who are obese and have diabetes or insulin resistance [3]. Adiponectin directly inhibits TNF- α which plays a role in tumor cell proliferation and angiogenesis [3,4]. Decreased concentrations of adiponectin and increased inflammatory and pathogenic mediators such as TNF- α , IL-6, PAI-1 and reactive oxygen species in NAFLD are claimed to play a role in this carcinogenesis [3,5]. Also, adiponectin decrease leads to increased insulin levels due to marked insulin resistance and increased IGF-1 [3,5]. IGF-1 has been shown to increase cellular turnover and inhibits apoptosis. It also leads to increase production of vascular endothelial growth factor which supports tumor growth [4,5]. That's why NAFLD and gastric cancer relationship needs more data. Nevertheless, there is not enough data to reveal possible link between the gastric cancer and NAFLD yet. In this regard we reviewed 1840 recent patients who underwent esophagogastroscope in our endoscopy unit in the last 6 months. We checked 15 patients who were diagnosed as distal gastric cancer and observed that NAFLD was present in 35.7% of the patients with distal gastric cancer (5/14) (Table 1), which was higher than the normal Turkish population.

This preliminary data based on a single center experience shows that NAFLD may be linked to gastric carcinogenesis. An increased understanding of the mechanisms of metabolic syndrome-induced carcinogenesis provides the development of new methods to prevent or treat gastric cancer. To our opinion new studies are necessary to clarify this association.

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Table 1. Features of 14 patients

Patient No	Sex	Age (years)	Hepatos-teatosis	Metabolic syndrome
1.	M	82	-	+
2.	M	66	-	-
3.	M	63	+	+
4.	M	56	-	-
5.	F	83	-	-
6.	M	56	+	+
7.	F	65	-	-
8.	M	60	+	+
9.	M	81	-	-
10.	M	74	+	-
11.	F	76	-	+
12.	F	59	+	+
13.	F	85	-	-
14.	M	72	-	-

M: male, F: female

Renal cell carcinoma with metastasis to the testis

Dear Editor,

Renal cell carcinoma (RCC) constitutes approximately 85% of all primary malignant renal tumors. Histologically RCC arises from renal epithelium as a mixed adenocarcinoma. The most common histologic subtype is conventional clear cell carcinoma. It is estimated that approximately 30% of the patients have evidence of metastatic disease at presentation. The most common site of RCC metastasis is the lung. Moreover, liver, bone, adrenals, brain, the opposite kidney and subcutaneous tissue are frequent sites of metastasis. Testicular metastasis from RCC is a very rare condition and only a few cases are reported in the literature.

We present two cases of RCC metastasis to the testis arising from primary conventional clear cell histologic subtype which were successfully treated with radical orchiectomy.

A 61-year-old male presented with a painless palpable mass of the left testis. Two years ago he underwent radical nephrectomy for RCC. The pathology revealed RCC of conventional clear cell histologic subtype. He also underwent surgical removal of a metastatic mass located in the cervical spine. Physical examination confirmed a firm nontender mass in the left testis. AFP, β -hCG and LDH were within normal limits. Scrotal ultrasound revealed an intratesticular isoechoic mass with increased internal vascularity on color Doppler imaging. The patient underwent radical left orchiectomy and an orange-like color mass of 3.5X3X2.5 cm was explored. Pathological examination showed testicular RCC metastasis of clear cell subtype. Abdominal and chest CT proved that the patient was metastasis-free. No further treatment was necessary.

A 51-year-old male with a history of left radical nephrectomy due to RCC 5 years ago presented with a painless palpable mass in the left testis. Physical examination revealed a painless firm mass in the left testis. AFP, β -hCG and LDH were within normal limits. Scrotal ultrasound showed a well circumscribed isoechoic mass with increased internal vascularity located in the left testis. The patient underwent radical left orchidectomy and an orange-color mass of 5X4X3 cm was explored. Pathology confirmed RCC metastasis of clear cell histologic subtype to the testis. Abdominal and chest CT showed no further pathologic findings. No further treatment was necessary.

The incidence of secondary testicular tumors ranges from 0.3% to 3.6% with the most frequent primary site being the prostate [1]. Less common primary sites of testicular metastasis are lungs, melanomas, large intestine and kidney [2]. The actual rate of testicular RCC metastasis cannot be calculated as most articles in the literature are

case reports. The pathologic diagnosis of metastatic RCC to the testis almost always reveals clear cell tumor [3]. It is possible that the secondary testicular mass may be the initial clinical presentation of RCC [4]. Differential diagnosis can be difficult as secondary testicular tumors may mimic primary ones in gross appearance. Scrotal ultrasound, AFP, LDH and β -hCG should always be performed in all patients. Moreover age can play an important role in differential diagnosis as primary tumors usually happen in younger males. Both patients were treated with radical orchiectomy and are disease free for the time being. No further treatment was necessary. A possible mechanism of testicular metastasis secondary to RCC is retrograde venous seeding [5].

Surgical removal by radical orchiectomy is the best choice in the treatment of secondary testicular RCC tumors. An abdominal and chest CT scan should always be performed as in most cases testicular metastasis is accompanied by metastasis in other organs. If the patient is proven to be disease free after surgery no further treatment is necessary but a strict follow up program should be applied as there is a great risk of developing further metastasis in other organs in the future.

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Unexpected progression of hepatocellular carcinoma in a patient with inactive HBsAg carrier state: pulmocranial metastasis

Dear Editor,

A 60-year-old man presented with left sided hemiparesis during the last 4 days. He had a history of chronic hepatitis B (inactive HBsAg carrier state) with no regular hospital visits for the last 10 years. On physical examination, he was afebrile, with a blood pressure of 105/55 mm/Hg and a pulse of 88 beats per min. Neurological examination revealed hemiparesis of both upper and lower left-side extremities with no encephalopathy and flapping tremor. Full blood count and serum biochemistry including liver function tests were within normal range. The prothrombin time was 1.0 sec and the partial thromboplastin time 11.6 sec (10.5-14.5). HBsAg (+), HBeAg (-), anti-HBe (+), HBV DNA <79 IU/ml, Alpha-fetoprotein 4.6 (reference range: 0 - 8.1 ng/mL), and testing for hepatitis C, hepatitis D and human immunodeficiency virus were negative. An hyperechoic large mass (diameter 16 cm) and portal hilar lymphadenopathy was detected on hepatobiliary ultrasonography (US). Dynamic computed tomography (CT) of the liver was compatible with hepatocellular carcinoma (HCC) measuring 17 cm while portal and superior mesenteric veins were not infiltrated. Also, multiple pulmonary metastases (the largest being 4 cm) were detected on the thoracic CT. Cranial MR showed multifocal lesions, compatible with HCC metastases, in the posterior part of the right cerebral hemisphere with edema. Decompressive craniectomy was performed for brain edema and biopsies of the cranial lesion showed HCC similar to that found in the liver sampling. The patient refused to undergo further treatment. He died 1 month after his discharge from the hospital.

HCC is the most common type of primary liver tumor. Extrahepatic metastasis of HCC is rare (13%) [1]. Intrahepatic tumor size and vascular invasion are the main factors that increase the risk of metastasis [2]. Abdominal lymph nodes (53%), lung (55%) and bone (28%) are

the most common sites of metastases. Brain metastasis (0.65%) is an extremely rare location for HCC [3,4]. Thus, the AASLD Practice Guideline for HCC recommended surveillance of HBV carriers at high risk of HCC with US every 6-12 months [5]. In addition, physicians should be vigilant for HCC and its uncommon metastases in patients with a history of HBV.

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Hypothesis: Should prophylactic mastectomy be indicated for breast cancer in high risk women?

Dear Editor,

There is an old saying: "By studying the history we learn from the past, we understand better the present and foresee the future".

It's beyond any question that medical people try to exploit, with good will and according to the beliefs and

views of the time, everything for the benefit of humankind. All views based on scientific data are justified, but sometimes there are side-effects and costly consequences.

Breast screening - mammography is used for years according to the idea that cancer could be detected at an early stage and start its treatment, until we started counting the benefits and harms of such a procedure [1].

Prophylactic mastectomy in high risk subjects has started applying recently, but what its consequences will be ?

Cancer is a general disease of unknown cause, with local manifestations. The whole organism contributes and suffers from it. It develops and grows in every tissue and organ of the body except the heart for unknown reasons [2].

Paget in 1889 on one hand [3], speaking about cancer had said that the development and growth of the disease resembles a tree, whose seeds are carried to all directions but they can only live and grow if they fall on favorable and "fertile soil".

Beatson on the other hand in 1896 [4], reported that when as a young doctor was working in a big farm with cattle, he noticed that the shepherds were removing the ovaries of the cows in order to prolong the lactation period after cows' labor.

He got really astonished "how an organ being in a big distance from another one could influence the other's function"!

By prophylactic mastectomy, the first priority "fertile soil", the breast, is cleared out but the "tree" does not disappear and continues to sow seeds spreading them to all directions and which tries to find another "fertile soil" relative to the previous one, like ovaries, in order to be installed and grow.

With these thoughts in mind we become very circumspect in adopting prophylactic mastectomy in high risk women for breast cancer.

After all the woman is submitted to a big mutilating operation, mastectomy, removing an organ for which she is very sensitive. But even so, is she secured from the development of a secondary cancer, especially ovarian ?

If she is very eager to do something because she is afraid of her heredity and predisposition why not remove the ovaries instead ?

Removal of the ovaries is rather preferable for three reasons [4,5]:

In comparison to mastectomy it's a minor operation which can be done even by laparoscopy.

It influences, to a certain extent, the hormonal factor of cancer.

It has no influence on the appearance of the woman.

Last but not least, this has been already included in the National Comprehensive Cancer Network (NCCN) criteria for clinical practice (www.nccn.org/professionals). It is mandatory then, to be followed by all the physicians related to oncological clinical practice and especially in the oncological committees.

We don't like to be prophets of evil but we are afraid that the incidence of cancer in other organs related to breast, mostly ovaries, will be increased after prophylactic mastectomy.

The future will show.

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Extended upper sternectomy with curative intent for neglected papillary thyroid carcinoma in a fit 65-year-old man

Dear Editor,

Recently, the authors had to reconstruct the anterior chest wall immediately after an extended upper sternectomy with curative intent for neglected papillary thyroid

carcinoma in an otherwise fit 65-year-old man; a previous attempt to radical resection was abandoned 3 years ago due to technical difficulties, followed by unsuccessful treatment with radioactive iodine.

Vascular and plastic surgical colleagues were in-

volved; the on-table vascular ultrasound orientated us to the relation of the brachiocephalic vessels, and the plastic team performed bilateral pectoralis major (PM) flaps with lateral releases. The extended upper sternectomy involved the upper half of the sternum, the heads of the clavicles and the 3 upper ribs bilaterally, having to ligate the internal thoracic arteries. We covered the superior mediastinum with a commercially available XCM™bioprosthesis [1]. No bars, or other rigid prosthetic material were used on this occasion.

The patient was admitted to the Intensive Care Unit for postoperative monitoring due to the long duration of the operation. On the second postoperative day he unfortunately developed severe bilateral pneumonia with significant desaturation and the need for temporary mechanical ventilation. This was not considered to be connected to the sternectomy or any disturbance of chest wall movements/respiratory mechanics. There were no other complications and the patient was discharged on postoperative day 10 from the hospital.

Our main learning points from this case were:

a) Risk of death high, patient's wishes taken into account (We had previously offered him the completion operation when we saw first at 2.5 years following his first and failed attempt to manubriectomy at the original thyroidectomy operation. Due to his fear of the mortality and morbidity of the planned operation he had refused this offer first, but changed his mind after unsuccessful radio-iodine treatment).

b) Neglected case, as thyroid malignancies often

run an indolent course [2,3].

c) Imaging and on-table vascular ultrasound for risk management of brachiocephalic vessels.

d) Sacrifice of internal thoracic arteries as required.

e) Bioprosthetic material covered anteriorly with bilateral PM release flap always useful for covering anterior thoracic defects.

f) Extending the antimicrobial prophylaxis to 48 hours in future cases.

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Denosumab: Excellent response of metastatic giant cell tumor of the bone

Dear Editor,

Giant cell tumor of bone (GCTB) is a benign condition of the appendicular or axial skeleton. GCTB typically occurs in patients aged 20-40 years with a slight female predominance. The most common locations of GCTB are distal femur, proximal tibia and distal radius and accounts for 5% of all primary bone tumors. Although GCTB is a benign neoplasm, it has a propensity for aggressive local invasion and destruction. Metastatic disease at presentation is uncommon; only 3-4% of GCTB metastasize, primarily to the lungs, and surgery is the definitive therapy; however, recurrence varies from 10 to 75%, depending on the size and location of the lesion and the surgical intervention [1]. Theoretically, drugs that inhibit the osteoclast-like giant cells and the proliferating stromal cells should be effective against GCTB. The pathophysiological studies of GCTB show high concentrations of receptor activator of nuclear factor kappa-B ligand (RANKL) in the neoplastic stromal cells. Denosumab which is a new hu-

man monoclonal antibody against the RANKL has been shown to have a significant impact in GCTB due to antitumoral and antiosteoclastic activity [2].

In this report, we emphasize the complete response to denosumab in a patient with metastatic GCTB.

A 46-year-old male presented to the orthopedics clinic with left wrist swelling and pain in 2006. During physical examination a 40x30 mm painful mass was found. MRI revealed a lobulated 40x32x38 mm area in the scaphoid and lunate bone which was hypodense in T1 and heterogeneous in T2. Extensive excision following reconstruction surgery was performed and histology showed GCTB.

Local tumor recurrence occurred after 7 years. MRI showed a 40x30x30 mm mass in the left distal radius. The patient underwent surgical resection and pathology revealed recurrence of GCTB with angiolymphatic invasion. Further investigation with chest x-ray revealed multiple nodules in both lungs and thoracic computed tomography (CT) revealed subpleural and parenchymal metastatic round nodular lesions, the largest being 18x12 mm in the

anterior segment of the left upper lobe. Denosumab was administered due to unresectable lung metastasis (120 mg every 28 days subcutaneously). After 6 cycles of treatment significant regression of lung lesions was seen and wedge resection of the left upper lobe of the lung was performed. After 6 more cycles of denosumab the parenchymal metastatic lesions completely disappeared. No adverse reactions to denosumab were seen. Currently, the patient is been receiving treatment for 15 months without signs of local recurrence or new pulmonary metastases.

Despite different chemotherapy regimens and interferon alpha-2b, lung metastases after GCTB treatment generally have unfavorable outcome. Dramatic treatment responses in early studies were achieved with denosumab in recurrent or metastatic GCTB [3]. An open-label, phase II study showed that denosumab inhibits progressive bone destruction and metastatic progression in patients with unsalvageable GCTB [4].

In our case significant regression of lung nodules was achieved by monthly denosumab within 6 months. After ongoing treatment complete response was achieved. We agree with Thomas et al. [4] who suggest continuous denosumab treatment in cases of unsalvageable GCTB, particularly with pulmonary metastasis. Additionally, we believe that continued denosumab administration may have a positive therapeutic role in cases of non-salvageable GCTB and in the neoadjuvant setting where it might improve the surgical outcomes.

Denosumab seems to be a well tolerated drug in previous studies [2,4]. Most common side effects are hypocalcemia, hypophosphatemia, increased bone mineral density, risk for fracture and osteonecrosis. A phase 2 study evaluating the safety and efficacy of denosumab found adverse events related to long term treatment consistent with the known safety profile [5]. In our case, no hypocalcemia or hypophosphatemia were seen.

We believe that denosumab demonstrated good efficacy with decreased rates of disease progression and recurrence in both resectable and unresectable or metastatic GCTB disease. However, how long and how often should this treatment be continued, the effect of interrupting

treatment on relapse, and long term side effects need to be answered with future, long term randomized studies.

In conclusion, denosumab is a new efficient therapeutic option for patients with unresectable or metastatic GCTB as a neoadjuvant treatment. This remarkable case is encouraging and hopefully ongoing clinical studies will better define the role of RANKL pathways in this unusual neoplasm.

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Gastric cancer and gallbladder: single center experience

Dear Editor,

Gastric cancer has been proposed to be linked to gallbladder based on several mechanisms. First, *H.pylori* colonization is one of the major factors in the pathogenesis of distal gastric cancer [1,2]. Gastric carcinogenesis, starting from chronic active inflammation leading to atrophy and metaplasia of the gastric mucosa and finally dysplasia or

cancer is the outline of this process [1]. Similarly, many studies show a significant relationship between *H.pylori* and gallstones [2]. Additionally, recent data suggests that *H.pylori* spp. can be found in gallstones, bile and gallbladder tissue demonstrating chronic cholecystitis. Therefore, *H.pylori* eradication therapy was suggested for gallstone prevention [3]. On the other hand, gallstones per se may be linked with gastrointestinal tract cancer through in-

flammation or bile flow alterations leading to metabolic changes, although not enough data exists yet to establish this association [4]. Cholecystectomy is recommended in gastric cancer surgery by several authors but this is an issue of debate. That's the reason why gallbladder and gastric cancer relationship needs more data. In this regard we reviewed 15 recent patients with gastric cancer diagnosed in the last 6 months in our gastroenterology clinic. We checked the charts of each patient for age, sex, gastric cancer location at first gastroscopy and gallbladder appearance with ultrasonography (Table 1). We observed 40% (6/15) of these patients had distal gastric cancer. While 4 patients with distal gastric cancer had gallbladder problems, the patients with proximal gastric cancer had comparably normal gallbladder. All 6 patients with distal gastric cancer were *H.pylori*-positive. Based on this very few patient data we hypothesize a possible link between gallstones and distal gastric cancer. No doubt, further studies are warranted to elucidate this possible link.

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Table 1. Data of patients with gastric cancer

Patient no.	Age (yrs) / sex	Gastric cancer type (location)	Gallbladder appearance (ultrasonography)	Elective cholecystectomy
1.	73/male	Distal (antrum)	Normal	Not performed
2.	66/male	Proximal (fundus)	Normal	Not performed
3.	90/female	Proximal (corpus)	Normal	Not performed
4.	65/female	Proximal (corpus)	Normal	Not performed
5.	57/male	Distal (antrum)	Chronic cholecystitis	Performed
6.	59/male	Proximal (fundus)	Normal	Not performed
7.	62/female	Proximal(cardia)	Normal	Not performed
8.	65/male	Distal (antrum)	12 mm gallstone	Performed
9.	46/male	Proximal(corpus)	Normal	Not performed
10.	55/male	Distal (antrum)	Normal	Not performed
11.	71/male	Proximal(cardia)	Normal	Not performed
12.	68/female	Proximal (fundus)	Normal	Not performed
13.	81/male	Distal (antrum)	Chronic cholecystitis	Performed
14.	58/male	Proximal(cardia)	Normal	Not performed
15.	82/male	Distal (antrum)	Chronic cholecystitis	Performed

Ofatumumab in a chronic lymphocytic leukemia patient with graft versus host disease and relapse after mini-alloBMT

Dear Editor,

Non-myeloablative allogeneic stem cell transplantation can be an option for younger patients with chronic lymphocytic leukemia (CLL) with rapidly progressive disease. Although potentially curative, such an option has a high risk of treatment-related mortality and relapse, and

graft versus host disease (GVHD) is frequent [1].

We would like to report the case of a 55-year-old man, diagnosed with Binet B stage CLL in 2000 based on enlarged lymph nodes and lymphocytosis (25G/l) with typical phenotype: CD5+, CD19+, CD23+, FMC7- and weak sIgM kappa. CD38 expression was negative and cytogenetics

normal. The patient was in watchful waiting for 4 years, then, at a lymphocytosis of 120 G/l, treatment was started, consisting of 3 cycles of CHOP followed by 3 cycles of fludarabine, leading to complete remission. The patient relapsed a year later, receiving second line DHAP chemotherapy. At the third relapse, 3 years later, the patient was treated with rituximab in association with fludarabine and cyclophosphamide, and again a complete remission was obtained. Non-myeloablative allogeneic stem cell transplantation from a related donor was performed. Although treated with cyclosporine A and methotrexate to prevent GVHD, typical skin lesions appeared after two months and were treated with corticosteroids and cyclosporine A. One month later, the lesions disappeared leading to the progressive reduction of steroids. The effect was transient, and GVHD skin manifestations reappeared, treated with rituximab associated with cyclosporin A and topical corticosteroids. Eighteen months post transplantation, in a context of exacerbation of chronic GVHD, relapse was confirmed by the presence of circulating clonal CD5+ CD19+ B cells and enlarged lymph nodes. Ofatumumab was proposed aiming to target both leukemic and auto-reactive B cells. It was administered at the usual dose and schedule (300 mg, then 2000 mg weekly for 8 cycles, then 2000 mg monthly for 4 months) and was well tolerated, without notable toxicity. CD5+ CD19+ CLL cells soon became undetectable in the blood and marrow (Table 1) with rapid regression of adenopathies. Surprisingly, there was no improvement in the cutaneous status: the skin lesions of GVHD persisted, still treated with topical corticosteroids. Blood B cell depletion was not associated with changes in C4 fraction of the complement but we found a progressive diminution of the gamma fraction on serum protein electrophoresis, persisting during maintenance therapy, a common finding with monoclonal antibody therapy (Table 1).

Ofatumumab is a humanized anti-CD20 monoclonal antibody developed to target B cells, and used in fludarabine, rituximab, and/or alemtuzumab-resistant CLL pa-

tients [2]. Compared to rituximab, ofatumumab binds a distinct, membrane-proximal epitope, dissociates from its target at a slower rate, and is more effective to induce CLL B cell lysis, by at least three mechanisms: direct apoptosis, through antibody dependent cell death mediated cytotoxicity and complement-dependent cytotoxicity [3].

Use of ofatumumab in CLL patients relapsing after allogeneic stem cell transplantation was not reported to our knowledge, and represents an interesting option due to its limited haematological toxicity. Its efficacy in chronic GVHD remains an open question.

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Table 1. Evolution of blood and bone marrow parameters during ofatumumab therapy. W1-8: weekly doses, M1-4: monthly doses

	W1-	W2-	W3-	W4-	W5-	W6-	W7-	W8-	M1-	M2-	M3-	M4-
<i>Ofatumumab</i> (cycle - dose)	300 mg	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg	2000 mg
Total lymphocytes (G/l)	0.4	0.8	0.6	0.3	0.3	0.6	0.47	0.6	0.78	0.92	1	1.2
CD19+CD5+ (%)	4	<0.1			1	2			2			<0.1
Bone marrow				negative					negative			
BM phenotype									< 1% CD19+CD5+			
Gamma globulins (g/l)	7.2	5.6	5.8	4.5	5.5	5.3	4.9	4.5	4.1	3.9	3.5	3.5

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