Paid Progression of a Radiographic Para-Bronchial Abnormality after Hip Surgery
A Potential Case of Angiogenic Switch/Augmentation in a Patient with Lung Cancer

Authors
Ogugua N. Obi MD, MPH
Assistant Professor of Medicine
Department of Internal Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
Brody School of Medicine, East Carolina University, Greenville, NC 27834
obio@ecu.edu
No Conflicts of Interests.
Carlos J. Anciano, MD
Assistant Professor
Thoracic & Foregut Surgery
Department of Cardiovascular Sciences
Brody School of Medicine
East Carolina University, Greenville, NC 27834
Ancianoc14@ecu.edu
Consultant for Medtronic Corporation

Mark R. Bowling, MD
Corresponding Author
Department of Internal Medicine
Division of Pulmonary, Critical Care and Sleep Medicine
Department Of Cardiovascular Surgery
Division of Thoracic and Foregut Surgery,
Brody School of Medicine, East Carolina University, Greenville, NC 27834
bowlingm@ecu.edu
252-744-4650. phone
252-744-1115. Fax
Consultant for Medtronic Corporation, Genentech Pharmaceuticals, and Biodesix
Permission was given by the patient and the IRB of East Carolina University to submit the case report.

ABSTRACT:
Most human tumors arise and remain in-situ without progression and angiogenesis for months to years. "Angiogenic Switch" a term coined about 30 years ago, refers to the transition from pre-vascular hyperplasia to highly vascularized and progressively outgrowing tumor. The Angiogenic switch is controlled by changes in the fine-tuned balance between pro- and anti-angiogenic factors secreted either by tumor cells or by cells of the tumor microenvironment. Several pro-angiogenic factors have been elucidated, however emerging evidence shows that bone marrow (BM)-derived endothelial progenitor cells (EPCs) contribute to the angiogenic switch in tumor growth and metastatic progression. It has been suggested that tissue trauma, as experienced in surgical procedures, may initiate such changes resulting in rapid tumor progression. We present a case of what we believe to be an angiogenic switch after hip surgery.

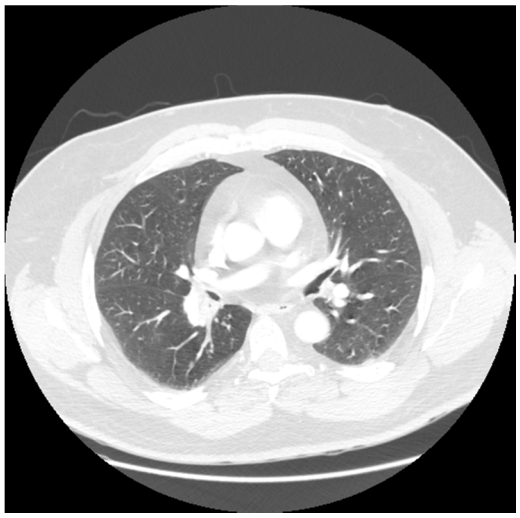
Introduction:

The current wisdom is that spontaneously arising tumor cells are usually not angiogenic at first [2]. Indeed, most human tumors arise and remain in situ without angiogenesis for months to years before switching to an angiogenic phenotype [1]. The term "Angiogenic Switch" (AS) coined in the late eighties, refers to a time-restricted event during tumor progression during which dormant tumor cells transition from pre-vascular hyperplasia to highly vascularized progressively outgrowing malignant tumor mass due to a shift in the delicate balance between pro- and anti-angiogenic factors in the tumor milieu [3] [4]. Clinically, the avascular phase usually corresponds to small and occult lesions of not more than 1-2 mm in diameter [4]. In the past decades, a plethora of angiogenic factors have been identified that directly or indirectly induce proliferation and differentiation of endothelial cells and hence tilt the balance of events towards pro- or anti-angiogenesis. Some of the angiogenic promoters include Vascular Endothelial Growth Factor-A (VGEF-A) [3] [5], Fibroblast growth Factor (FGF)-1 and -2 [6], Platelet Derived Growth Factor (PDGF)-B and C [7] [8] and Angiopoetin-2 (Ang-2). In more recent times, it has become increasingly evident, that different subsets of bone marrow (BM)-derived cells including endothelial progenitor cells (EPC), hemangiocytes, macrophages, monocytes and other BM-derived hematopoietic cells contribute to the initiation and maintenance of the switch [9] [10]. Once a cancer has become established, the issue of tumor growth and metastasis then becomes paramount. Several factors have been postulated to promote tumor growth. From antiquity until the 18th century, the subject of cancer progression and management was dominated by the philosophy and deep belief, that surgery disseminated cancer cells and potentially worsened disease [16]. Although cancer treatment and surgical oncology has since undergone several radical revolutions and refinements, it remains well known, that excessive surgical stress augments the growth of residual cancer cells and can potentially promote tumor metastasis [15]. Tsuchiya et al, showed, that increased surgical stress augments lung cancer metastasis in mice injected with colon 26-L5 carcinoma cells. The group demonstrated that the number of lung metastases, was directly proportional to the degree of surgical stress and that this was mediated via surgical stress-induced expression of proteinases in the target organ of metastasis [15]. Hofer SOP et al [17], demonstrated that several of the growth factors that play a role in surgical wounding and wound healing, have also been implicated in tumor growth and progression. Some of these factors include epidermal growth factor (EGF), transforming growth factor (TGF)-α and TGF-β, basic fibroblast

growth factor (bFGF), insulin-like growth factor (IGF I and IGF II) and platelet-derived growth factor (PDGF). We believe that the case below is a clinical representation of both processes. **Case Presentation:**

A 60-year old ex-smoker (35 pack years, quit 9 years prior) was admitted to our hospital with a 3-week history of cough and 2 episodes of scant streaky hemoptysis. He described long-standing history of chronic sinus congestion and upper airway cough syndrome and was recently started on albuterol MDIs by his primary care provider for COPD. He denied fever, chills, weight loss, night sweats or prior episodes of hemoptysis. There were no urinary symptoms, skin rash, known TB exposures or underlying history of bleeding diathesis. He was not on any anticoagulants or anti-platelet medications. Chest CTA showed prominent abnormal bronchial wall thickening and severe luminal narrowing of the proximal right lower lobe (RLL) bronchus.

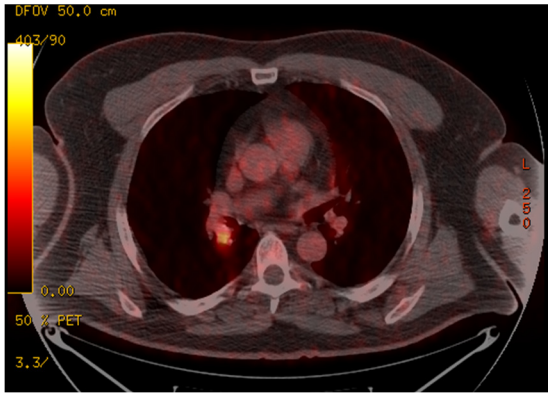
Figure 1.



Thoracic Computed Tomography (CT) scan before the hip surgery showed prominent abnormal bronchial wall thickening and severe luminal narrowing of the proximal right lower lobe (RLL) bronchus

There was no mediastinal, hilar or axillary lymphadenopathy. Patient underwent a bronchoscopy for airway inspection revealing a 50% narrowed but patent right superior segment bronchial ostium. Mucosa appeared inflamed, but there was no active bleeding or endobronchial lesion seen. A bronchioalveolar lavage (BAL) specimen was obtained and patient was scheduled for a PET scan with plans for a repeat bronchoscopy with trans-bronchial biopsies. His BAL cytology showed few atypical squamous cells with benign respiratory epithelial cells. PET scan (Figure 2) showed an abnormal hypermetabolic area (SUV 5.9) in the right posterior hilar distribution corresponding to the previously identified area of soft tissue prominence and bronchial narrowing.

Figure 2.

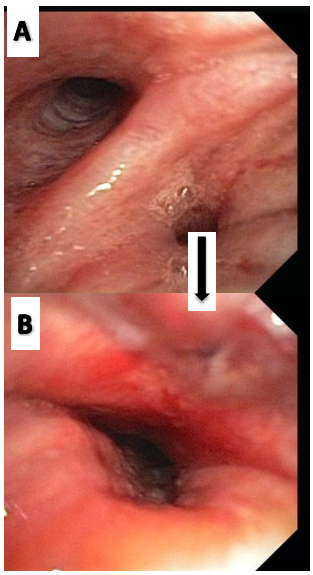


Pre hip surgery Positron Omission Scan demonstrating a hypermetabolic

area (SUV 5.9) in the right posterior hilar area

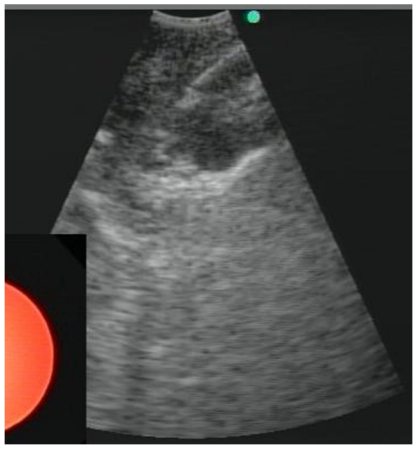
Based on the results of the PET/CT scan, a repeat bronchoscopy with Endobronchial ultrasound (EBUS) guided transbronchial needle biopsies was scheduled. In the interim however, patient underwent an uneventful right total hip replacement surgery (THRS) 18-days after his initial bronchoscopy (three days after his PET/CT scan). At his repeat bronchoscopy 8-days after THR surgery, his findings were markedly different from the initial bronchoscopy. There was now > 80% narrowing of the R superior segment bronchial orifice and a pearl colored exophytic endobronchial lesion, was now present at the bronchial orifice (Figure 3). EBUS guided needle biopsies (figure 4) and brushings of the abnormal areas were obtained and pathology revealed moderately differentiated squamous cell carcinoma of the lungs (p63 positive, TTF-1 and CK7 negative). Patient was staged clinically as T1, N1 M0 and underwent definitive curative RLL and RML lobectomy.

Figure 3



Pre (A) and post (B) hip surgery bronchoscopy demonstrating a complete occlusion of the right lower lobe superior sub segment and endobronchial lesion as compared to the patent pre surgery bronchoscopy (see arrow).

Figure 4.



Endobronchial Ultrasound Image of the Mass and fine needle aspirate.

Discussion:

The role of pro and anti-angiogenic factors in tumor development and progression has been well described in the literature. The exact mechanism however, by which a small dormant lesion suddenly becomes rapidly progressive and invasive remains unclear. It has been well shown, that surgery may hasten tumor progression and metastasis. This is not surprising, considering that tumors have long been referred to as "wounds that do not heal" [22] and many of the growth factors that play a role in surgical wounding and wound healing also play significant roles in tumor growth and metastasis resulting in earlier tumor recurrence following primary resection of a known cancer, or tumor growth after invasive diagnostic procedures [17]. In addition, the expression of pro-angiogenic factors is increased in the presence of certain stressful conditions such as hypoxia, glucose deprivation, formation of reactive oxygen species and cellular acidosis [4] [23] – all of which are potential peri-operative events; further emphasizing the potential role of surgery and other invasive procedures in rapid tumor growth. It is notable, that our patient underwent THR – a surgery that involves significant manipulation of the bone and bone marrow. The Bone marrow serves as a reservoir of Endothelial Progenitor Cells (EPC), which can be mobilized following tumor challenge. These BM-derived EPCs promote angiogenesis by paracrine secretion of pro-angiogenic factors and by luminal incorporation into a subset of sprouting nascent vessels [9] [10]. Nolan et al [11] described increased angiogenesis following recruitment and incorporation of BM-derived EPCs into the lumen of tumor neovasculature. Jin et al, [12] showed that BM derived EPCs are involved in the progression from micro metastases to macro metastasis – largely by angiogenesis and neovascularization. We propose that both the stress, and nature of surgery (THR) by manipulation of the bone and bone marrow potentially triggered an angiogenic switch/ augmentation that accelerated tumor growth and progression by releasing several BM derived pro-angiogenic factors and stimulating the growth factors involved in wound healing. Unfortunately it is difficult to prove that indeed our case represent a true case of tumor progression due to angiogenic switch, but the clinical scenario, timing of the THR and evidence of the rapid tumor growth as noted by bronchoscopy, does support this hypothesis. Regardless, If possible, we suggest that patients with suspected early malignancy that is to undergo invasive surgical procedures should consider pursuing a definitive diagnosis and treatment plan for the suspected tumor first. It may also be worthwhile to consider pre-operative chemo or radiation therapy in situations where invasive procedures cannot be avoided. Further studies are

needed to fully understand this concept and guide medical management in these situations.

Conclusion:

We have presented a case of a 60-year old ex-smoker with an incidental finding of a RLL lesion that underwent rapid growth after an elective hip replacement surgery. We postulate that the stress of surgery, as well as the release of BM-derived pro-angiogenic factors from manipulation of the bone marrow likely provoked an angiogenic switch/ augmentation that triggered rapid tumor growth by recruitment of numerous bone marrow derived pro-angiogenic factors and release of growth factors associated with surgical wound healing into the local tumor milieu.

Bibliography

[1] D. Ribatti, B. Nico, E. Crivellato, A. Roccaro and A. Vacca, "The History of the angiogenic switch concept," *Lukemia,* no. 21, pp. 44-52, 2007.

[2] J. Folkman, K. Watson , D. Ingber and D. Hanahan, "Induction of angiogenesis during the transition from hyperplasia to neoplasia," *Nature,* no. 339, pp. 58-61, 1989.

[3] V. Baeriswyl and G. Christofori, "The angiogenic switch in carcinogenesis," *Seminars in Cancer Biology,* no. 19, pp. 329-337, 2009.

[4] G. Bergers and L. E. Benjamin, "Tumorigenesis and the Angiogenic Switch," *Nature Reviews Cancer,* vol. 3, pp. 401-10, 2003.

[5] N. Ferrara, H. Gerber and J. LeCouter, "The biology of VGEF and its receptors," *nature Medicine,* vol. 9, pp. 669-76, 2003.

[6] Friesel and T. Maciag, "Molecular mechanisms of angiogenesis:fibroblast growth factor signal transduction," *FASEB J,* vol. 9, no. 10, pp. 919-25, 1995.

[7] E. Battegay, J. Rupp, L. Iruela_Arispe, E. Sage and M. Pech, "PDGF-BB modulates endothelial proliferation and angiogenesis in vitro via PDGF beta-receptors," *Journal of Cell Biology,* vol. 125, no. 4, pp. 917-28, 1994.

[8] R. Cao, E. Brakenhielm, X. Li, K. Pietras, J. Widenfalk, A. Ostman and et al, "Angiogenesis stimulated by PDGF-CC, a novel member in t he PDGF family, involves activation of PDGFR-alphaalpha and -alphabeta receptors.," *FASEB J,* vol. 16, no. 12, pp. 1575-83, 2002.

[9] G. Dingcheng, D. Nolan, K. McDonnell, L. Vahdat and R. Benezra, "Bone marrow-derived endothelial progenitor cells contribute to the angiogenic switch in tumor growth and metastatic progression," *Biochimica et Biophysica Acta,* pp. 33-40, 2009.

[10] D. Gao and V. Mittal, "The role of bone-marrow-derived cells in tumor growth, metastasis initiation and progression," *Trends in Molecular Medicine,* vol. 15, no. 8, pp. 333-343, 2009.

[11] D. J. Nolan, A. Ciarrocchi, A. S. Mellick, J. S. Jaggi, K. Bambino, S. Gupta, E. Heikamp, M. R. McDevitt, D. A. Scheinberg, R.

Benezra and V. Mittal, "Bone marrow-derived endothelial progenitor cells are a major determinant of nascent tumor neovascularization," *Genes Dev,* no. 21, pp. 1546-1558, 2007.

[12] H. Jin, A. Aiyer, J. Su, P. Borgstrom, D. Stupack, M. Friedlander and J. Varner, "A homing mechanism for bone marrow-derived progenitor cell recruitment to neovasculature," *J. Clinical Investigation,* vol. 3, no. 116, pp. 652-662, 2006.

[13] H. G. Kopp, S. T. Avecilla, A. T. Hooper and S. Rafii, "The bone marrow vascular niche: home of HSC differentiation and mobilization," *Physiology (Bethesda),* no. 20, pp. 349-356, 2005.

[14] T. Asahara, T. Takahashi, H. Masuda, C. Kalka, D. Chen and H. Iwaguro, "VEGF contributes to postnatal neovasculirization by mobilizing bone-marrow derived endothelial progenitor cells.," *EMBO J,* no. 18, pp. 3964-3972, 1999.

[15] T. Yasunori, S. Shigeaki, I. Yoshioka, Y. Ohashi, M. Matsuo, Y. Harimaya, K. Tsukada and I. Saiki, "Increased surgical stress promotes tumor metastasis," *Surgery,* no. 133, pp. 547-55, 2003.

[16] M. Baum, R. Demicheli, W. Hrushesky and M. Retsky, "Does surgery unfavorably perturb the "natural history" of early breast cancer by accelerating the appearance of distant metastases?," *European Journal of Cancer,* no. 41, pp. 508-515, 2005.

[17] S. Hofer, G. Molema, R. Hermens, H. Wanebo, J. Reichner and H. Hoekstra, "The effect of surgical wounding on tumor development," *European Journal of Surgical Oncology,* no. 25, pp. 231-243, 1999.

[18] J. Coffey, J. Wang, M. Smith, D. Bouchier-Hayes, T. Cotter and H. Redmond, "Excisional surgery for cancer cure:therapy at a cost," *Lancet oncology,* vol. 4, pp. 760-768, 2003.

[19] S. Ben-Eliyahu, G. Page, R. Yirmiya and G. Shakhar, "Evidence that stress and surgical interventions promote tumor development by supressing natural kiler cell activity," *INternational Journal of Cancer,* no. 80, pp. 880-888, 1999.

[20] A. Shiromizu, T. Suematsu, K. Yamaguchi, N. Shiraishi, Y. Adachi and S. Kitano, "Effect of laparotomy and laparoscopy on the establishment of lung metastasis in a murine model.," *Surgery,* no. 128, pp. 799-805,

2000.

[21] R. Demicheli, M. W. Retsky, W. J. M. Hrushesky, M. Baum and I. D. Gukas, "The effects of surgery on tumor growth: a century of investigations," *Annals of Oncology,* vol. 19, p. 1821–1828, 2008.

[22] H. Dvorak, "Tumors:wounds that do not heal. Similarities between tumor stroma generation and wound healing," *New England Journal of Medicine,* no. 315, pp. 1650-1659, 1986.

[23] P. L. Marjon, E. V. Bobrovnikova-Marjon and S. F. Abcouwer, "Expression of the pro-angiogenic factors vascularendothelial growth factor and interleukin-8/CXCL8 by human breast carcinomas is responsive to nutrient deprivation and endoplasmic reticulum stress," *Molecular Cancer,* no. doi:10.1186/1476-4598-3-4, 2004.