

marrow supports the paraneoplastic nature of the hypereosinophilia in this patient. Peripheral blood eosinophilia occurs in several medical conditions such as allergic disease, parasitic infection, certain forms of vasculitis, and medications, as well as in leukemia and lymphoma.¹⁻³ However, eosinophilia in solid malignancies is rarely reported.⁴ It has been described in many kinds of solid tumors including thyroid,¹¹ genitourinary,¹² gastrointestinal,¹³ hepatocellular,¹⁴ breast,¹⁵ and lung carcinoma.^{2,8} In lung malignancies, it has been described in all types of cancer including small-cell,¹ adenocarcinoma,¹⁶ and squamous cell.⁹ However, it is rarely reported in large-cell carcinoma.^{4,5,17} The pathogenesis of this phenomenon is controversial. Numerous explanations have been postulated. Bone marrow stimulation via circulatory factors secreted by the tumor itself is the most acknowledged and accepted theory.⁴⁻¹⁰ Interleukin-5, GM-CSF, and G-CSF are the most implicated factors studied. Other involved factors are still possible. In our patient, the hypereosinophilia along with the aggressive course of the disease might all be related to the increased level of certain immunomodulator and growth factor, although these cytokines had never been measured. Finally, this study as well as previous ones supports that eosinophilia in the context of malignancy generally reflect its aggressiveness and very poor prognosis.^{5,10,18-20} In fact, this patient already presented with metastatic disease before any treatment. Despite chemotherapy, his clinical course was marked by rapid progression and fatal outcome. Rare exceptions to this rule, where eosinophilia is associated with good prognosis or is not correlated with the prognosis, are reported in the literature.^{13,15}

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Sirolimus in Metastatic Renal Cell Carcinoma

In October 2005, a 65-year-old man was referred to our clinic with the finding of a 7 cm right anterior lower-pole renal mass that had been discovered incidentally during a computed tomography angiogram of the abdominal aorta for evaluation of claudication. Computed tomography (CT) scans of the abdomen and chest showed no definitive evidence of metastatic disease and in November 2005, a laparoscopic radical nephrectomy was performed. The procedure was difficult as the tumor appeared to be somewhat adherent to the vena cava. Pathological analysis revealed a unifocal 6.8 cm renal cell carcinoma (RCC) invading into the sinus adipose tissue. The RCC was of the clear-cell type, Fuhrman grade 3, and despite removal of all the sinus fat, the sinus margin was positive. The patient recovered well from the surgery, and in February 2006, an enhanced abdominal and pelvic CT scan as well as plain films of the chest showed no evidence of tumor. However, by August 2006, bilateral pulmonary nodules and a

2.2 cm liver mass were observed. Past medical history was significant for cerebrovascular accidents (CVA) in 1999 and 2002 with residual verbal apraxia, as well as perioral and right hand numbness. The patient had extensive vascular disease with an occluded right carotid artery and 50% occlusion of the left carotid artery, and areas of stenosis in multiple arteries in the pelvis and lower extremities. Other relevant history included hypertension, hyperlipidemia, a 90 pack-year history of smoking (quit in 2002), and a history of micturition syncope resulting in a subdural hematoma, which was evacuated and left no sequelae. The patient presented with liver and lung metastasis nine months after the resection of a primary RCC. The possibility of conducting a biopsy was discussed, but the patient elected not to, and this was reasonable, as both the pattern of metastasis as well as the timing of his characteristics were not unusual for an RCC.¹

Several treatment options are available for front-line treatment of patients with metastatic clear cell RCC,² including sunitinib and temsirolimus.^{3,4} Sunitinib is a small-molecule kinase inhibitor that

improves progression-free survival, but which is associated with cardiovascular adverse events.⁵ During sunitinib clinical development there were two deaths due to CVA (data on file; Pfizer Inc, New York, NY), and patients with a history of CVA in the year prior were excluded from the phase III trial. While the frequency of arterial thrombotic events with sunitinib is estimated at less than 1%, given the potentially devastating consequences of an additional CVA, the benefit did not seem to outweigh the risk. Temsirolimus is a specific inhibitor of the mammalian target of rapamycin complex 1 (mTORC1; generically referred to as mTOR), which functions as an atypical serine/threonine protein kinase and is involved in the regulation of many cellular processes including in the regulation of protein translation.⁶ However, how inhibition of mTORC1 affects RCC is not known; some evidence suggests that it might involve the down-regulation of the hypoxia-inducible factor transcription factor.⁷ Temsirolimus has been shown to improve patient overall survival, but does not appear to increase objective response rates compared with interferon- α .⁴ Importantly the temsirolimus phase III trial was targeted to patients in a poor prognosis category. Overall, temsirolimus was well tolerated and there were fewer patients with serious adverse events in this group than among those treated with interferon- α .⁴ Importantly for our patient, temsirolimus does not appear to increase the risk of arterial thrombosis; in fact, mTORC1 inhibitors have been used to coat endovascular stents and might decrease the risk of stent occlusion.⁸ Our patient was in a lower risk category compared with the patients in the temsirolimus phase III trial (risk factors: disease-free-

interval < 1 year, and multiple sites of metastasis), and while some evidence suggest that patients with fewer risk factors may benefit less from temsirolimus,⁹ temsirolimus seemed the best option. The patient had a history of hyperlipidemia, which might be exacerbated by mTORC1 inhibitors, but a lipid panel was normal. At the time of presentation however, temsirolimus had not been approved by the US Food and Drug Administration, and it could not be obtained. Repeat CT scans were conducted in November 2006 and these showed marked disease progression; the dominant metastasis in the left lobe of the liver had in 3 months increased from 2.2 cm to 6.3 cm in diameter, and a new 2 cm lesion in the right hepatic lobe had appeared. While the patient remained asymptomatic, given the rapid rate of tumor progression, therapy seemed warranted. Sirolimus, like temsirolimus, is an inhibitor of mTORC1 (in fact, mTOR derives its name from sirolimus, which is also called rapamycin); it had been approved by the US Food and Drug Administration in 1999 for immunosuppression following renal transplantation and was therefore commercially available. Of note, temsirolimus is a sirolimus ester (compare chemical structures in Figs 1A and 1B) that is hydrolyzed to sirolimus in patients, such that 74% of the circulating drug following weekly temsirolimus is actually sirolimus^{10,11} (compare Figs 1C and 1D [Adapted/redrawn with permission from Macmillan Publishers Ltd]). At trough, circulating sirolimus concentrations exceed those of temsirolimus by approximately a factor of ten (compare drug levels at 168 hours in Figs 1C and 1D).¹² Following a discussion of this information with the patient, it was decided to proceed with sirolimus, and this was

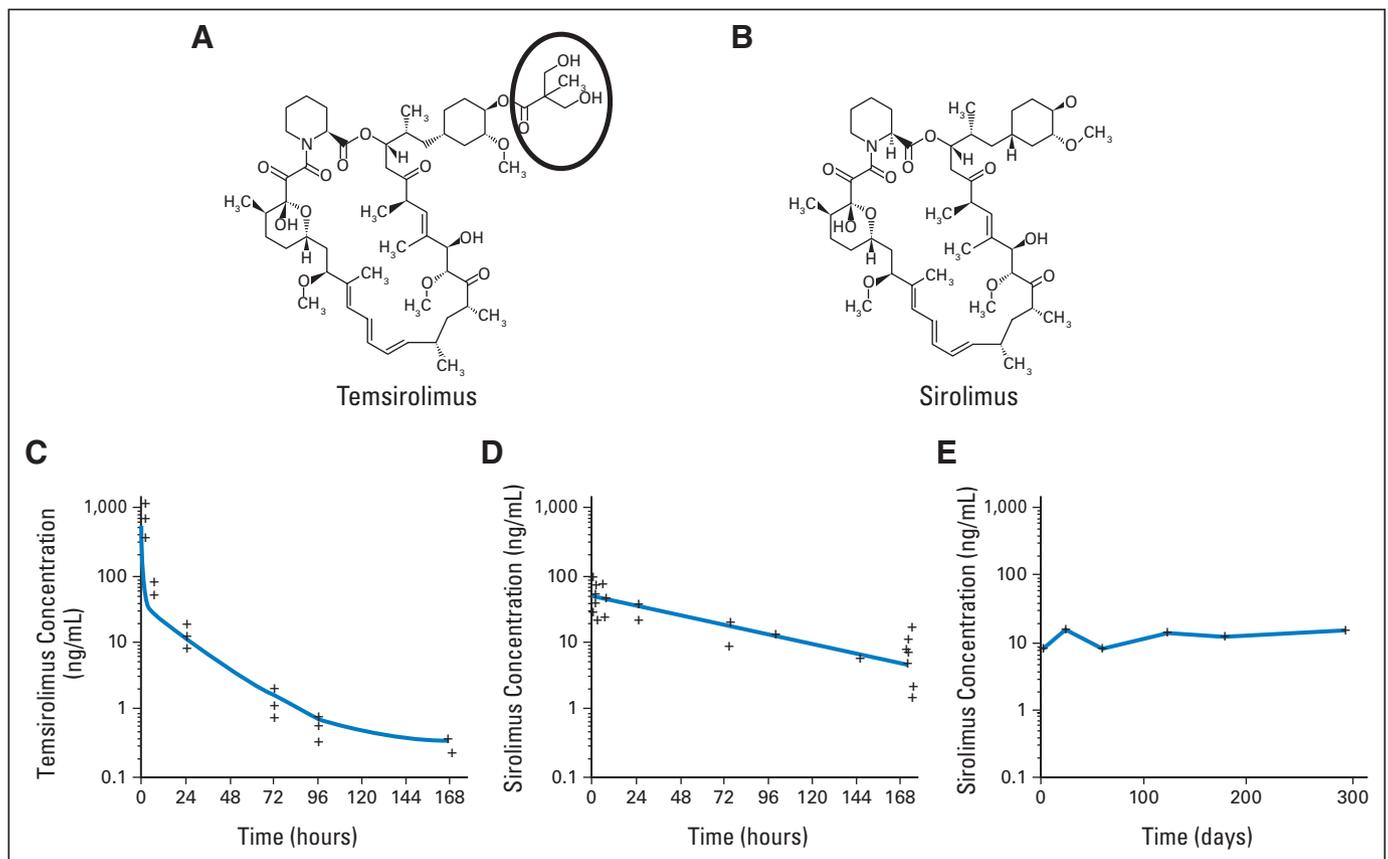


Fig 1.

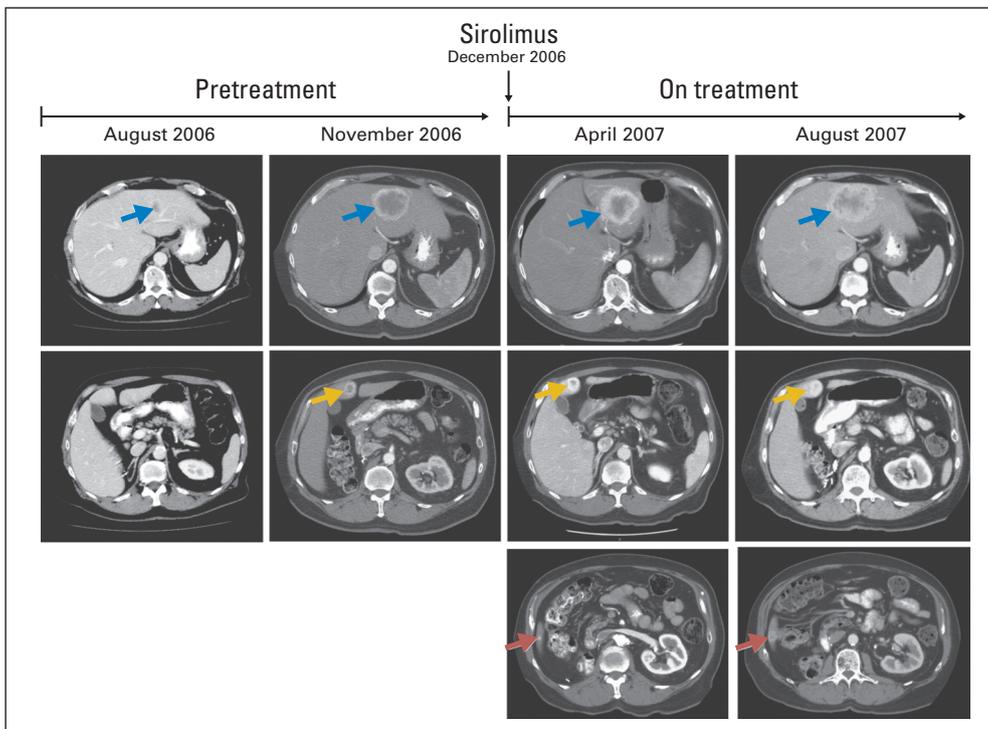


Fig 2.

started in December 2006. Sirolimus is metabolized through the cytochrome P450, family 3, subfamily A, polypeptide 4 (CYP3A4), which is involved in the metabolism of a large number of drugs, and while the patient was taking no CYP3A4 inducers or inhibitors, other drugs were adjusted to minimize the number of agents metabolized by this enzyme and diminish the probability of drug-drug interactions. Importantly, while the patient was not on warfarin, warfarin is also a CYP3A4 substrate and doses might need to be adjusted in patients taking (tem)sirolimus. Sirolimus was initiated at a dose of 6 mg orally daily without a loading dose, and sirolimus levels were measured at trough after a week on treatment (when levels are believed to stabilize). At this time, sirolimus levels were found to be 8 ng/mL (Fig 1E). This level was within the range of trough sirolimus levels observed after the administration of weekly temsirolimus (compare trough sirolimus levels in the patient at 8 days in Fig 1E with trough sirolimus levels 168 hours after temsirolimus administration in Fig 1D), and the sirolimus dose was maintained. Throughout the treatment course, sirolimus trough levels were between 8 and 15.5 ng/mL (Fig 1E), and sirolimus was well tolerated. CT scans of the abdomen and pelvis in February 2007 showed the hepatic and pulmonary metastasis to remain stable. Repeat CT scans in April showed a new 0.5 cm right hepatic lesion, but otherwise stable metastasis in the liver and lungs (Fig 2 and data not shown) and sirolimus was continued. In June and August 2007, CT scans of the chest and abdomen showed metastasis to remain stable in size, and no new lesions were observed (Fig 2 and data not shown). Thus, the size of the lesions in the liver and lungs did not appear to substantially change over a period of 8 months, and the patient remained on sirolimus. These results were in stark contrast with pretreatment scans, which showed the dominant left hepatic lesion to have tripled in diameter and interval development of a second 2 cm left hepatic lesion in the span of 3 months (Fig 2). In contrast to the effects observed in the liver and lung, disease progression was readily

evident in the brain. A pretreatment magnetic resonance imaging scan in December 2006 showed a 4 mm occipital metastasis. The lesion was asymptomatic and without appreciable edema and radiation therapy was withheld. A repeat magnetic resonance imaging scan in February 2007 showed a doubling in the diameter of the occipital brain metastasis, surrounding edema, and an adjacent new 2 mm metastasis. Stereotactic radiosurgery was administered with good control. However, in August 2007, multiple brain metastases were found. In conclusion, oral sirolimus can achieve trough levels comparable with those found following the administration of temsirolimus. In our patient, compared with a pretreatment analysis, the administration of sirolimus was associated with a marked decrease in the rate of tumor progression outside the CNS. While this was not the case for our patient, one setting in which sirolimus might be more advantageous than temsirolimus is in patients with renal failure who are on hemodialysis (HD). Temsirolimus has not been studied in HD patients, and HD might only affect circulating levels of temsirolimus modestly because of its relatively large molecular weight (1030 Da), its large volume of distribution, and its being bound to blood-formed elements. However, because temsirolimus is typically dosed weekly, the effects of HD on circulating drug levels are likely to be more profound with temsirolimus than for oral sirolimus, which is administered daily.

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Trichomegaly of the Eyelashes After Lung Cancer Treatment with the Epidermal Growth Factor Receptor Inhibitor Erlotinib

A 57-year-old white woman who had never smoked presented with a history of isolated coughing for several months. Computed tomography scans of the chest demonstrated a 2.5 × 4.5-cm right-middle-lobe tumor, widespread bilateral pulmonary nodules consistent with metastases, and enlarged lymph nodes in the subcarinal, paratracheal, and prevascular regions (Fig 1, yellow arrows). Fine-needle aspiration biopsy of the lesion revealed bronchogenic adenocarcinoma. Magnetic resonance imaging of the brain revealed four subcentimeter metastatic lesions with minimal edema. Polymerase chain reaction–based sequencing of DNA of the epidermal growth factor receptor (*EGFR*) gene revealed an 18-base pair deletion in exon 19 of the *EGFR* gene, which has been previously reported in patients with lung tumors that responded to erlotinib.¹⁻³ The patient received whole-brain radiation therapy with a total of 30 Gy in ten fractions. She then received systemic front-line therapy with single agent erlotinib (standard oral dose, 150 mg). Her disease demonstrated a major response to erlotinib; the diffuse pulmonary nodules disappeared 6 weeks after she started therapy, while the primary right-middle-lobe tumor shrank down to 1.0 × 4.0 cm² 2 months later and remained stable for over 1 year (Fig 1). Thirteen months after the initiation of systemic therapy, clear progression of disease was noted, with development of new pulmonary nodules and an increase in the size of the right-middle-lobe tumor. Since the addition of bevacizumab did not provide better tumor control, further treatment was switched to the chemotherapy doublet of carboplatin and paclitaxel, which reinduced a durable partial response. During her therapy with erlotinib, the patient experienced a mild rash on her face, chest, and back, which was treated with emollients and topical clindamycin. She had mild paronychia, which improved after topical therapy. The patient experienced alopecia after brain radiotherapy, and it persisted with very slow hair regrowth while she was receiving erlotinib. She had growth of dark,

thick, coarse hairs on the dorsal aspect of her fingers as well. Three weeks after starting erlotinib, the patient noticed an accelerated growth of her eyelashes, which interfered with her wearing glasses because the lashes pushed against the lenses. She had to trim her eyelashes with scissors on a weekly basis. Close examination revealed marked bilateral coarse, thick, elongated irregular growth of the eyelashes, with marked darkening and curling of the terminal ends (Fig 2). These changes resolved after erlotinib was discontinued when disease progressed.

Hypertrichosis of the eyelashes, or eyelash trichomegaly, was originally described in the setting of rare congenital conditions such as Oliver-McFarlane syndrome,⁴ oculocutaneous albinism type 1,⁵ or familial hypertrichosis.⁶ Although it may be encountered in the context of generalized acquired hypertrichosis,⁷ hypertrichosis of the eyelashes is more often an isolated finding. It is defined as an increase in the length, thickness, stiffness, curling, and pigmentation of existing eyelashes.⁸ Acquired trichomegaly of the eyelashes has been repeatedly described in case series of patients infected with HIV type 1⁹ or in association with uveitis.¹⁰ Trichomegaly has been reported in some patients secondary to therapy with a drug such as the antiretroviral agent zidovudine (a reverse transcriptase inhibitor),¹¹ and is usually associated with poor tolerance to the drug. Topical ocular hypotensive (antiglaucoma) agents such as latanoprost¹² and bimatoprost¹³ have on rare occasions caused trichomegaly of the eyelashes. Other ocular topical treatments such as cyclosporine¹⁴ and systemic therapy with the anticonvulsant topiramate⁸ also have been reported to cause trichomegaly. The condition was noted in some recipients of solid organ transplants who were given cyclosporine¹⁵ or tacrolimus.¹⁶ Acquired trichomegaly was reported in isolated cases of patients with dermatomyositis¹⁷ and systemic lupus erythematosus¹⁸ (Table 1). In cancer patients, trichomegaly must be distinguished from a rare paraneoplastic syndrome, the acquired hypertrichosis lanuginosa, characterized in adults by the abnormal growth of lanugo-type hair, confined to the face and neck and concomitant with the spread of an internal malignancy.^{19,20} Trichomegaly can occur in patients with cancer in the setting of a paraneoplastic syndrome,²¹ or secondary to anticancer