

growth factor or in the presence of only trace quantities of the factor. Such a mechanism fits nicely with the observation by the Cambridge group that all patients with polycythemia vera who had the mutation had cells in their blood that formed erythroid colonies in vitro in the absence of erythropoietin.⁴ The net result could be chronic low-grade but excessive stimulation of erythropoiesis, a characteristic of polycythemia vera.

Why are some patients with polycythemia vera heterozygous and others homozygous for the mutation? The evidence suggests that homozygosity for the mutant gene results from the mitotic recombination of chromatids bearing the mutation and not from a second mutation in a mutant heterozygous lineage. Either way, the homozygosity may be the result of two distinct steps, the first of which is enough to produce features of the disease.

And what of the patients with polycythemia vera, essential thrombocythemia, or myelofibrosis who apparently do not have *JAK2* mutations? Can we expect to find another unifying mutation equivalent to this one? If so, will it be in the *JAK-STAT* pathway or independent of it?

Even if Dameshek was right to link these myeloproliferative disorders, how exactly could the same acquired mutation in the *JAK2* gene cause three clinical entities that are more or less distinct? The simplest explanation is merely to postulate the existence

of other genetic abnormalities that either are pre-existing or occur after the acquisition of the *JAK2* mutation. Other possibilities must also exist.

And what is the basis for the progression from a seemingly benign condition (polycythemia vera) to acute leukemia in some, but not all, cases? The question brings to mind the analogy with chronic myeloid leukemia, a disease associated with an activated tyrosine kinase, which also starts gently and progresses to an aggressive termination. Extending the analogy, one may speculate that a small molecule that inhibits normal and mutant *JAK2* could prove clinically useful in these myeloproliferative disorders, as it has so impressively in chronic myelogenous leukemia. At the very least, this newly identified molecular lesion will form the basis of a new classification. But it seems likely that patients will also eventually derive substantial benefit from the discovery.

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2. James C, Ugo V, Le Couedic J-P, et al. A unique clonal *JAK2* mutation leading to constitutive signalling causes polycythaemia vera. *Nature* (in press).
3. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase *JAK2* in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell* (in press).
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They Sent Me Here

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An interview with Dr. Ofri can be heard at www.nejm.org.

"Ramonita Ortega," I called out to the crowded waiting room. A slim, 50-ish woman with crisply trimmed gray hair followed me into my office.

"They told me to give you this," she said, smiling and shrugging, as she pushed an envelope across the desk toward me.

I've always been intrigued by who "they" are — those mystery people referred to with such assumed authority and universality. Particularly in a large city hospital, in which the staff is mammoth and con-

stantly changing, "they" constitute a particularly encompassing force.

I glanced at her chart before opening the envelope. Ms. Ortega had no medical history, except for a three-pack-a-day smoking habit she'd given up several years ago. She had gone to the dermatology clinic recently for the removal of a sebaceous cyst on her back. The cyst was not healing well, so she was headed toward ambulatory surgery for a more formal excision. She had been to presurgical testing, and I assumed that she had been sent to the medical clinic for a routine pre-op evaluation.

The envelope was unsealed, and Ms. Ortega watched, slightly bemused, as I fumbled with the

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papers to extricate them. On top was a handwritten consult sheet from the presurgical-testing clinic.

“Please eval for LUL mass,” was scrawled on top; the rest of the page was blank.

LUL mass? An icy edge sliced through the air and I blinked twice, not entirely sure that I had read correctly.

A mass in the left upper lobe of the lung? The “routine visit” atmosphere was suddenly annihilated by the specter of cancer, and the pleasantries of a getting-to-know-you meeting dissipated with austere efficiency.

I looked up from the page and caught Ms. Ortega’s eyes. They were an unsullied brown, with only a scattering of wrinkles gracing their edges. I withdrew my gaze quickly, self-consciously. It was clear that Ms. Ortega and I were now intimates in a different realm. We now shared an awful knowledge and the grim resignation that went with it. I couldn’t bear to hold her gaze in mine.

I turned to the attached x-ray report. “Indication: routine preop in an otherwise healthy female. Results: left upper lobe ovoid mass visualized, along with several satellite lesions. Suspicious for malignancy.”

“Damn,” I whispered to myself, laying the papers down and unconsciously pushing them into the general mess on my desk.

I forced myself to look up at this healthy-appearing woman, but all I could see was the path of CT scans, biopsies, chemotherapy, living wills, morphine drips, hospice. I shut my eyes again, but the vision remained: the beginning of a grisly journey. The path was cut, and we were already several steps along it.

I opened my eyes, dreading the necessity to begin but grateful that at least that first horrible hurdle — the actual telling of the bad news — was already past, and there were some practical tasks ahead of us, concrete items that were easier to focus on.

“Well,” I said, swallowing, trying to sound as matter-of-fact as possible. “Well, we’ll just start with a CT scan; that’ll help us get a better look at that lung mass. Radiology is on the third floor,” I continued, reaching, almost too quickly, for the form in my drawer. My fingers jittered as I filled in the blanks. “Have you ever had allergies to contrast dye in CT scans?” I asked.

Ms. Ortega hadn’t moved in her chair since I’d started speaking. Her smile from my earlier clumsiness was still there, though it had pulled inward slightly. I imagined that this chilling reminder of the reason for her visit with me was sinking in, clouding over the nice rapport that we’d been establishing. I wanted to respect this difficult moment, so I completed the CT form in silence.

Finally, she spoke. “Lung mass?” she said slowly. “What . . . ,” she paused, “are you talking about?”

The pen clattered as it dropped from my hand. There was an agonizing blankness as I stared dumbly at her.

“Didn’t they . . .” I was unable to unlock my eyes from hers. I groped for the x-ray report I’d pushed aside, suddenly desperate to retrieve the “evidence.” “Didn’t they . . . tell you?”

“No,” Ms. Ortega said, in a voice that seemed far too calm, blinking as if to clear her vision. “I came back for my results and they just handed me an envelope. They said I should give it to you.”

Her eyes searched my face, and her cadence and tone softened to one more of surprise than hurt. “They just said that my surgery was canceled.”

I finally located the x-ray report and clamped my sweaty fingers around it.

“Left upper lobe ovoid mass,” the black letters reiterated. They *had* to have told her about it when they canceled her surgery. They *had* to have told her about it when they sent her to the medical clinic.

How could they not? I could feel my anger rising like bitter bile.

The innocence of Ms. Ortega’s surprise both pained and perplexed me. I wondered why she hadn’t peeked into the unsealed envelope to read the information she had been instructed to ferry to me. She was so trusting of “them” that she didn’t stop to question.

I watched Ms. Ortega’s face, waiting for it to contort into anger, indignation, at least annoyance. But it didn’t. The faintly raised eyebrows, the lips half-parted, suspended in what might have been mid-word, suggested surprise and bewilderment. Her poise — perhaps it was shock — lent an eerie calm to the room.

I, on the other hand, was furious at “them.” How could they have done this to Ms. Ortega? And how could they have put me in this position — of talk-



ing to a patient with the mundane familiarity of comrades in disease, only to run slipshod over one of the most vulnerable moments in medicine?

I imagined a faceless “they” scrolling through the pre-op lab results in the computer, stumbling onto the x-ray report. I wondered whether there was a catch in their breath when they saw the report. Did they avert their gaze when they told Ms. Ortega that her surgery had been canceled and that she needed to see a new doctor? Did they fumble for an explanation as they spoke to her, something benign enough so she wouldn’t get scared but urgent enough so she would keep the appointment? Did they notice a raw pinch in their stomach as they slid the x-ray report into the envelope for her?

Or did they simply leave the envelope at the front desk for her to pick up?

Didn’t they bear some responsibility, as the first physicians to have laid eyes on the x-ray report?

But “they” were a mysterious and anonymous gray zone. They’d made the appropriate referral to an internist but had slunk away from the messier part.

“Ms. Ortega . . .” I reached across the desk and slid my hand over hers. “The x-ray of your chest shows a mass.” Ms. Ortega’s brown eyes remained fixed on mine. “I can’t tell you for sure what this mass is, but cancer is a strong possibility.”

No medical history, except for a three-pack-a-day smoking habit she’d given up several years ago. I felt the warmth of her hand calm mine. “Whatever this mass is, we need to find out as soon as possible.”

Ms. Ortega’s face relaxed. It settled into an odd, slight smile. “I’m with you on that one, doctor. Whatever God has in store for me, I want to know.”

I held onto her hand, waiting — again — for shock, anger. But it didn’t come. Did she not put two and two together and realize that the previous doctors had withheld this news? Or did the anvil edge of a possible cancer diagnosis overshadow this issue that I seemed so fixated on? Perhaps she was used to an anonymous “they” in her life and simply wasn’t perturbed by it.

For the remainder of our visit, Ms. Ortega remained reserved, focused on the tasks at hand. I asked several times if she had any questions or concerns, but she shook her head. Her main worry was

that she would have to miss another day of work in order to have the CT scan.

All I could think of was that soon enough she wouldn’t be able to work at all. But I couldn’t say that. I couldn’t tell her that I was 99 percent convinced that it was cancer, most likely metastatic. Not, at least, until I had a biopsy result. But that wouldn’t stop me from making an oncology appointment for her.

I suddenly wondered whether I was acting like “them”: withholding some information, making referrals to specialists. I rationalized that I had been honest about the possibility of cancer and that there was no way to say for sure until the biopsy.

But still, I knew.

I knew. And I didn’t share my certainty with her.

The visit ended, unsettlingly, on the same even keel on which it had started. Our rapport was smooth, the treatment plan clear, the ends neatly — bizarrely — tied up. I found myself trembling from the incongruity of it, my rage at “them” threatening to spill over. They had been in possession of the information; how could they not have told her?

I showed Ms. Ortega to the door, shook her hand, wished her well. I wanted to apologize on behalf of “them,” on behalf of us, on behalf of the controlling forces of the universe, for the ineptitude we had shown her so far and for the unfairness of being selected for this disease. I wanted to promise that henceforth she would be treated with perfect sensitivity and that we would eradicate her disease. But I couldn’t predict how the next set of doctors would behave, and, of course, I couldn’t alter the unforgiving dictates of tumor biology.

Mostly, though, I wanted her to be angry, to share my rage.

As our hands slipped from their grasp, I realized that I was being selfish. My anger was *my* issue — not hers, if she didn’t want it to be. Ramonita Ortega was entitled to her own interpretations, her own defenses, and her own rhythm of striding forth in the world. Perhaps her priorities were, understandably, elsewhere right now. Who was I to impose?

But when the door closed, I seethed.

(Identifying details have been changed to protect the patient’s privacy.)