Over the course of their history, osteopathic medical colleges and hospitals have not been research-oriented, and many have not even been research-friendly. One problem is that the number of individuals in the osteopathic medical profession who have devoted a significant portion of their time to research has historically been small. Correspondingly, overall research productivity as measured in publications has not been considerable, internal dollars devoted to infrastructure to support research has not been a high priority, and the securing of external funding to support research projects has been limited.

In this article, I want to analyze why research has not been adequately incorporated in the mission or functions of osteopathic institutions. I will also examine the unintended consequences of this failure with respect to the education of osteopathic medical students and to the beliefs and practices of osteopathic physicians. Further, I will offer a rationale as to why osteopathic institutions need to develop and foster more ambitious research commitments. Finally, I want to explore practical ways for osteopathic institutions to better contribute to intellectual and scholarly inquiry.

**Historical context**

In 1910, Abraham Flexner authored a report entitled “Medical Education in the United States and Canada,” which was financed and published under the auspices of the Carnegie Foundation. In his detailed school-by-school account, Flexner excoriated most of the medical colleges of the day. He decried low matriculation standards, substandard quality of instructors, insufficient basic science laboratories, poor clinical training, inadequate financing of schools, a lack of meaningful relationships between colleges and affiliated universities, and a paucity of scientific inquiry and research at most colleges. Following the model of German universities and the specific American example of Johns Hopkins University’s medical school, Flexner asserted that research and clinical practice should be “one in spirit, method, and object.” Most medical school faculty, he argued, should be involved in research. “Research,” said Flexner, “is required of the medical faculty because only research will keep the teachers in condition.”

In the decades following this report, several reforms that Flexner advocated took hold in allopathic medical schools. This resulted in part from higher and more enforceable accreditation standards by the American Medical Association and the adoption of more stringent requirements for licensure by state medical boards. Prior to World War II, research in allopathic medical schools grew significantly both in terms of basic science and clinical disciplines. Medical schools allocated resources to improve and expand their research capabilities and their principal teaching hospitals. Schools recruited faculty members more often on the basis of research potential, and these faculty members received tenure and promotion based on research productivity. After World War II, the scientific output of allopathic medical schools and their teaching hospitals grew enormously, particularly because of the creation of the National Institutes of Health (NIH) and the establishment of large private foundations that supported biomedical research.

As part of his survey of medical education, Flexner also visited osteopathic medical colleges and excoriated them, not on the basis of theory and practice, but with respect to standards and education. As for research in the colleges, that was insignificant or nonexistent. Flexner wrote, “Let it be stated with all possible emphasis that not one of the eight osteopathic schools is in a position to give training as osteopathy itself demands....No effort is anywhere made to utilize prosperity as a means of defining an entrance standard or developing the ‘science.’” Granting all that its champions claim, osteopathy is still in its incipience. If sincere its votaries would be engaged in critically building it up. They are doing nothing of the kind.”

Although Flexner’s osteopathic critics argued effectively that some of his facts were incorrect, his arguments overdrawn, and his perspective prejudicial, they could not or did not refute some of his major conclusions. And while osteopathic medical schools in the decades thereafter made some improvements in standards, facilities, and curriculum, change was far less swift and less comprehensive than that of allopathic institutions. In addition, the goals were different. Under the umbrella of “science,” allopathic medical schools increasingly produced specialists, subspecialists, and researchers, whereas osteopathic medical schools, under the umbrella of “service,” continued their principal—if not sole—mission of producing general practitioners for underserved areas.

**Osteopathic research infrastructure**

If research was to flourish in osteopathic medical colleges, several related conditions had to be met. First, there had to
be a scholarly environment; second, there had to be motivated faculty trained in research methods; third, there needed to be adequate institutional support to carry out research (that is, facilities, equipment, access to patients, and support personnel); and fourth, there needed to be time and money available to research-oriented faculty. While allopathic medical schools after the Flexner report increasingly were able to meet all these conditions, osteopathic medical schools had a hard time doing so.

With respect to scholarly environment, none of the osteopathic medical colleges prior to the late 1960s was university-affiliated. This was in marked contrast to the allopathic medical profession. One of the principal missions of a comprehensive university is to conduct research as well as to teach. A comprehensive university offers more than a course of education; it embodies the "life of the mind." It offers the potential and reality for continuous dialogue and collaboration with faculty elsewhere on campus. Institutions such as these provide access to and interaction with graduate students, as well as greater resources than smaller universities and colleges. As freestanding institutions, osteopathic medical colleges were, in comparison to their allopathic counterparts, "little worlds." Also, because of their single-minded mission of producing generalist physicians—however laudable that goal may have been—osteopathic colleges were not by and large scholarly places. In fact, to put it bluntly, they were more like vocational schools in their overall approach to education.

Unlike allopathic medical schools, which greatly expanded their full-time basic science and clinical faculty to secure research talent, osteopathic schools after the Flexner report continued to rely on part-time paid faculty and volunteers as the bulk of their clinical instructors. These clinicians were community physicians who for the most part had neither interest nor background in research. Prior to World War II, and increasingly thereafter, osteopathic schools were able to employ PhDs to teach the basic sciences. However, the numbers of such PhDs remained small when compared with allopathic institutions. Also, the question of whether these faculty would be interested in or able to do research was dependent in large part on institutional commitment and resources available from osteopathic medical schools.

It was the ability of MD-granting institutions to obtain new and dramatically increased sources of funding through university support, state revenues, and philanthropy that allowed them to dramatically expand the number of full-time basic scientists and clinicians on their faculty and to provide the latter with the resources they needed to conduct research. On the other hand, osteopathic medical schools did not appreciably expand their funding base until the late 1960s. In addition to the lack of university-affiliated osteopathic medical schools, none of the osteopathic colleges were state schools, nor did they benefit significantly from outside philanthropy.

For decades, osteopathic institutions lived a hand-to-mouth existence, heavily dependent on tuition and contributions from alumni. Limited resources went to improving the educational infrastructure. A valuable monies went to building, equipping, and maintaining laboratories for teaching—not for conducting laboratory research. On the clinical side, the theoretical possibilities for research were expanded with the large increase in the number of osteopathic hospitals established during and after World War II. However, because clinical research had not been incorporated in the mission of osteopathic medical schools, it is hardly surprising that so little research activity was carried out in hospital settings.

Prior to the late 1960s, pockets of basic scientists and clinicians who were interested and capable of carrying out research did exist. But even when such individuals were available, they were handicapped not only in terms of limited resources, but also by having limited time to engage in scholarly pursuits. Because osteopathic institutions were able to afford only a few basic scientists, such professionals were hired as teachers first and foremost, and they were expected to function as generalists who could teach the most if not all their respective disciplines. These PhDs spent many hours in lectures, labs, and other student-related activities. They worked in isolation from others in their disciplines, had little or no access to graduate students, and had to make do with less-than-adequate facilities and equipment. That the Kirksville College of Osteopathic Medicine, beginning in the 1940s and extending onward, was able to develop a modest but nonetheless significant research program relating to the phenomenon that became known as "somatic dysfunction" is a remarkable testament to the skills and tenacity of J. Stedman Denslow, DO, Irwin Korr, PhD, and their associates being able to make full advantage of limited resources and time to carry out their investigations. But this was the exception not the rule.

The modern era

The establishment of the first university-based and state-supported osteopathic medical school at Michigan State University in 1969 was a significant event in the history of the profession. In subsequent years, osteopathic schools became constituent colleges at four other comprehensive state universities, and two free-standing taxpayer-supported osteopathic medical colleges were created in two states. In addition, new osteopathic schools were established at four privately supported universities, while five osteopathic colleges—both new institutions and longstanding ones—evolved into health science universities where the osteopathic school was but one of a number of colleges producing health professionals. Currently, only four of the 19 osteopathic medical schools operate as private, freestanding colleges. This new mix of organizational models created the prospect of a new emphasis on and more possibilities for research.

Indeed, the establishment of new osteopathic schools and the expansion of existing institutions in the 1970s were spurred by federal and state capitation monies. This government funding poured directly into college coffers with the goal of producing more physicians to address a feared practitioner shortage. Colleges could spend this substantial new source of revenue any way they wished—including developing a corps of researchers. Thus, both public and private osteopathic medical colleges
had greater opportunity than ever before to develop sustainable research programs.

The research infrastructure and capacity of osteopathic medical schools has improved overall, though the gains at individual institutions vary widely. The state university-based schools like the one in Texas, which have significantly greater budgets, can employ a larger cadre of basic scientists than other osteopathic colleges. As these universities already had a commitment to research, as well as publication and grant expectations with respect to its scientists, issues of lab space and resources were never a question of "if," but rather "how much." In addition to the university-based colleges, other osteopathic medical schools devoted a good portion of their increased revenues toward new laboratory space, equipment, and the hiring of additional basic scientists. However, these other osteopathic colleges had a greater likelihood of making their limited number of new hires cover broad curricular needs. They simply did not have as many resources to build concentrations of scientists in one or more specific areas, so they had difficulty creating true research teams. In addition, the cessation of federal and state capitation funding in the 1980s put a halt to the hiring of new researchers and basic scientists in some cases.

Few osteopathic colleges currently approach the number of basic scientists seen at equivalent-sized allopathic medical schools, and few appear to secure external funding or generate publications at anywhere close to the rate typical of M D-granting schools. In 1998, osteopathic schools received only $24.2 million in total research awards, $8.6 million of which was from NIH. If one treated the 19 osteopathic medical schools as a single institution, it would still rank No. 202 with respect to NIH funding.

Certainly the record of osteopathic medical colleges in securing external sources of research funding could have been far greater had there been a commensurate effort by clinicians at these schools in pursuing scientific research projects. At some schools, such as Michigan State, clinical research was given appropriate emphasis. Unfortunately, clinicians at many schools were not expected to engage in research activity. In decisions of promotion and tenure at such schools, faculty were evaluated almost exclusively with respect to teaching, board certification, and service. In addition, the number of full-time clinicians associated with osteopathic medical colleges has been, with some exceptions, very small. Typically, osteopathic institutions have established a concentration of clinical faculty only in family medicine and osteopathic manipulative medicine, and these practitioners tend to be heavily involved in teaching and clinical practice.

As the colleges over the past two decades divested themselves of ownership of their teaching hospitals, they essentially became 2-year schools, thus disengaging themselves from hospitals that could have been the sites for clinical research activities. Further weakening the clinical research infrastructure potential in recent years has been the dramatic number of closures of other osteopathic hospitals around the country.

Overall, recent statistics on the number of full-time faculty at DO- and M D-granting institutions revealed there was but an average of 73 full-time faculty in osteopathic medical schools compared to an average of 716 full-time faculty at allopathic medical schools. Just considering workforce issues alone, it is not surprising that osteopathic faculty continue to be stretched with respect to teaching and service, and have less time than allopathic college faculty to engage in scholarly activities. Although osteopathic colleges have been able to raise their educational standards, thereby producing osteopathic graduates who in many ways are indistinguishable in terms of overall quality from their allopathic counterparts, the educational orientation of osteopathic colleges continues to be largely vocational. This approach has significant unintended consequences with respect to public recognition of osteopathic medical schools and with regard to osteopathic student attitudes and behaviors.

Unintended consequences

Elsewhere I have noted that this profession suffers from what I call "osteopathic invisibility syndrome." Despite the more than 100-year existence of some osteopathic medical colleges and the greater number of practicing osteopathic physicians in recent years, only a small percentage of the American public knows what osteopathic medicine is. With some exceptions, osteopathic medical colleges are not generally known or sufficiently appreciated by the communities in which they are located or which they serve—certainly nowhere close to the recognition and reputation of allopathic medical schools. Part of the reason is that allopathic colleges and their teaching hospitals are more newsworthy. They are places of greater scientific inquiry. New discoveries in the basic sciences and in the diagnosis and treatment of disease add enormously to the prestige and perceived social value of an institution. Osteopathic schools may produce physicians and surgeons that serve society well, but this and of itself may not be of particular interest to the media or to the general public.

By not developing their research infrastructure, osteopathic colleges not only have been largely unable to secure federal or other research grants, they also have been unsuccessful in attracting philanthropic gifts from wealthy individuals and foundations that wish to support biomedical advances and breakthroughs. As a result, osteopathic schools continue to be funded principally through either one or two sources of funding—tuition and state appropriations.

Just as groundbreaking research excites the public, it can also motivate college students in choosing the medical schools to which they will apply. It is not necessary that these prospective medical students desire to conduct research per se; however, they may well judge the quality of the education they will obtain based on whether the institution they are considering contributes to fundamental knowledge. By not institutionalizing research programs on their campuses, osteopathic colleges are discouraging some of the best and brightest students from entering the profession.

Osteopathic colleges have certainly been oriented more to the "application" of knowledge than to its "creation." This only fosters the attitude on the part of osteopathic medical students that only the
content and practical experience that directly relate to becoming a clinician are important. While the clinical track should continue to be the principle focus of osteopathic medical schools, it should not be the only focus. Osteopathic medical colleges should be encouraging the “life of the mind” and providing support for some of their students to become researchers and teachers. Many osteopathic medical schools are too narrow in their mission, and this does not contribute to the multiple and broader needs of this profession.

The inability to institutionalize research, particularly clinical research, at osteopathic institutions has, over the years, weakened the acculturation, socialization, and distinctive beliefs and practices of osteopathic students and graduates. For osteopathic medicine to be what I have elsewhere called a “parallel and distinctive” profession, it must generate its own original literature. And yet, in the various clinical subjects—family medicine, internal medicine, obstetrics and gynecology, pediatrics, and so on—the principle authors of the research articles that osteopathic students read are almost invariably allopathic physicians. How distinctive can the osteopathic profession be if it merely borrows from and does not significantly contribute to scholarly publications? What is the message that is being given to osteopathic students?

Nowhere in this profession is the need for controlled clinical research more critical than in the area of osteopathic manipulative medicine (OMM). And yet, what exists is a comparably meager scientific literature based primarily on small sample sizes. Answering the question of whether OMM alone or in conjunction with other interventions is of value in maintaining or restoring people to health in specific conditions should be a paramount goal in osteopathic medical schools and hospitals. Basic scientists, bio-engineers, and social scientists—as well as osteopathic clinicians—should be involved in answering these questions, and osteopathic students should see this commitment and participate where appropriate. Students’ education in OMM should be rooted in research. Demonstrations in electromyographic and other objective measurements should underlie any hands-on instruction in techniques. This profession cannot afford an OMM curriculum that relies on a philosophy uncritically tested by research, and on an advocacy rooted primarily in anecdote.

Indeed, practitioners and third-party-payers are increasingly relying on “evidence-based” medicine as a means to determine what should be the standard of care for specific conditions. This ongoing trend should be a wake-up call to this profession that if it wishes to employ a distinctive osteopathic approach to the healthcare needs of its patients, it must demonstrate through outcomes studies the value of this distinctiveness. Yet there is currently little activity in osteopathic colleges and hospitals with respect to performing outcomes research.

Solutions

Osteopathic medical colleges and hospitals need to become places where research can be institutionalized more fully in their overall mission. Research is not a luxury for this profession: it is a practical necessity. Osteopathic medical schools and hospitals should become more visible in society. They need to become better funded. They need to be places where distinctiveness can flourish. They should be in a position to attract the most qualified faculty, students, and practitioners.

I believe there should be a series of national meetings attended by representatives of the American Osteopathic Association (AOA), the American Association of Colleges of Osteopathic Medicine (AAMC), the American Osteopathic Healthcare Association (AOHA), the American Academy of Osteopathy and the other specialty colleges, as well as osteopathic foundations to examine how a research mission can be better integrated into existing educational programs under the auspices of this profession—and how such a mission can be encouraged well into the future. These groups need to go beyond recognition of the problem; they need to devise practical and effective strategies to meet the challenge.

At the college level, the leadership of each school should, in its planning efforts, identify ways to increase its existing research programs. Each osteopathic college, in addition to working toward an environment in which research plays a significant and expanding role, should identify and give enhanced support to at least one area of excellence in which collaboration by basic and other scientists can focus on a specific research area. This will require an effort to hire faculty that goes beyond the need to simply “cover the curriculum.” Such an effort can be supported through general college funds as well as the creation of endowed chairs. The Osteopathic Heritage Foundation of Columbus, Ohio, for example, has just made such a gift to one school.

Also, the development of osteopathic postdoctoral training institutions (OPTIs) in the past few years offers the profession the possibility of strongly linking college-based basic, social, and clinical scientists with research-friendly practitioners at osteopathic and allopathic inpatient and outpatient settings. For the first time in the history of the profession, there is now the opportunity to attract large numbers of patients for clinical research projects based on the collective size of institutions involved with each OPTI. Ironically, although the number of osteopathic hospitals overall has dramatically declined in recent years, the clinical infrastructure for osteopathic physicians through OPTIs possesses its greatest potential for research than ever before.

Currently, planning efforts are under way by the Osteopathic Research Taskforce to develop a mechanism for collecting clinical practice data from large numbers of office-based practitioners throughout the profession, including uniquely osteopathic findings. This data would certainly be interesting and potentially useful for some purposes, including the development of practice guidelines. Obviously, such data-gathering and entry must be rigorously and continuously inspected for completeness and accuracy. I hope this effort moves forward cautiously, as difficult methodological issues still need to be resolved. For example, I
believe any recording of distinctly osteopathic findings on SOAP notes would be of limited if of any value for purposes of scientific research and peer-reviewed publication if they do not undergo interexaminer reliability or are not objectively measured through instrumentation. Therefore, before the osteopathic profession heavily invests in and implements this ambitious project, it should obtain assurances from experienced and distinguished external researchers that the data collected can be satisfactorily used for the research purposes intended by its advocates.

In my view, the most important clinical research task for this profession in the next several years is to steadily increase the number of well-trained osteopathic clinical researchers currently based at its colleges, hospitals, and OPTIs. Such individuals are critical to developing and building the necessary research infrastructure.

To accomplish this latter goal I would recommend that the profession give serious consideration to the development of a “Clinical Research Certificate Program.” This program could be created under the auspices of and funded through AACOM with possible participation by the AOA. This certificate program could be modeled on the AOA Certificate Program in Health Policy, which is administered by Ohio University, funded by the Osteopathic Heritage Foundation, and is now completing its seventh class. Each year, 10 to 12 osteopathic physicians sponsored by their respective colleges, hospitals, or OPTIs would go through a yearlong clinical research certificate program held monthly at various sites on weekends. Required reading assignments and learning activities throughout the year would be part of the curriculum. The fellows would become familiar with the basic methods and tools necessary to plan and conduct controlled clinical research. Fellows would learn how to prepare and write reports of their findings for publication, and they would learn grant-writing skills. Faculty and guest lecturers of such a research certificate program would consist of experienced researchers in the basic, social, and clinical sciences. The faculty would assist the fellows in launching pilot projects and would serve as continuing resources and mentors even after the conclusion of the certificate program. The graduates of this kind of program would be guaranteed support and resources by their sponsoring institutions so they could conduct their own specific research projects and perhaps be given formal appointments to develop clinical research more generally at their colleges, hospitals, and OPTIs. The relationships that are formed by the participants during their fellowship year will encourage multi-institutional projects.

A program like this would not be very expensive to develop and maintain if all the colleges involved with AACOM underwrote its funding. And if this program had been initiated at the time of the development of the AOA Health Policy Fellowship, there would be today more than 60 osteopathic clinicians who already would be significantly benefiting the research agendas of their sponsoring institutions. Many of these individuals would today be active contributors to the Journal of the American Osteopathic Association as well as to nonosteopathic scientific publications. Many might well be engaged in research projects that could be funded through federal and foundation dollars as well as by the AOA.

As for the AOA, I believe it should strive to continually increase the amount of money available to fund promising pilot research projects. Grants should be awarded solely on the basis of scientific merit as determined through a peer-review system. If research proposals do not meet rigorous criteria typical of the NIH or the National Science Foundation, the projects associated with those proposals should not be supported. AOA grant priorities should be based on whether a project, if carried out, could attract other sources of funding and lead to publications in the peer-reviewed literature. Funding to support projects that do not meet such criteria, however much they are rooted in a distinctively osteopathic approach, is money unwisely spent.

Conclusion

The osteopathic medical profession must commit itself to research. It must go beyond mere words of support for the idea of scientific inquiry and move on to build the infrastructure that will support and enhance such activity. Applying for highly competitive development grants from prestigious funding agencies without this infrastructure already in place may simply be an exercise in frustration.

Osteopathic medical colleges and hospitals have long served the American people by producing qualified physicians and surgeons and by providing quality healthcare services. But osteopathic institutions have an additional obligation: They need to be places that can generate new knowledge, including discoveries that can benefit patients.

Osteopathic medicine must be “researched and demonstrated.” It must show where and to what extent its distinctive approach to healthcare has value. To do so would increase its visibility and recognition not only to the scientific community but also to its patients and the public at large. For osteopathic medicine to move forward, it must be evidence-based. The studies that can provide this evidentiary foundation can only come from within the profession. It is the absolute responsibility of this profession to provide the researchers and resources to accomplish this goal and, as a result, ensure the future of osteopathic medicine.

References


Case report

Non-Hodgkin’s lymphoma in a patient with human immunodeficiency virus

MASSOUD MAHMOUDI, DO, PhD
DAVID CONDOLUCCI, DO
NATHAN FREED, DO

A 38-year-old woman with human immunodeficiency virus who was recently diagnosed with gastric ulcer presented to the hospital with nausea and vomiting of 1 month’s duration. Work-up of patient led to a diagnosis of diffuse, large B-cell non-Hodgkin’s lymphoma. The patient underwent six cycles of chemotherapy, and repeated endoscopy and biopsy failed to reveal malignancy. She remains in remission 23 months posttreatment. Management of patients with human immunodeficiency virus and concurrent malignancy remains a challenge. The primary care physician plays a central role by collaborating with infectious disease and oncologist specialists to formulate a management plan.

(Key words: human immunodeficiency virus, non-Hodgkin’s lymphoma, case report)

Dr Mahmoudi is a clinical assistant professor in the Department of Internal Medicine, University of Medicine and Dentistry of New Jersey School of Osteopathic Medicine, and in private practice (allergy) in San Francisco, Calif. Dr Condolucci is a chief in the Division of Infectious Diseases, and Dr Freed is an associate professor of medicine and chief in the Division of Hematology and Medical Oncology at the University of Medicine and Dentistry of New Jersey School of Osteopathic Medicine, Kennedy Memorial Hospitals University Medical Center, Stratford, NJ.

Correspondence to Massoud Mahmoudi, DO, PhD, 2211 Post St, Suite 301, San Francisco, CA 94115.

E-mail: ma0003@dnamail.com

Non-Hodgkin’s lymphoma (NHL) is one of many diseases that complicate the lives of patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). At times, diagnosis of NHL in patients with AIDS is challenging. One of the greatest problems that arises is when a patient with HIV presents with nonspecific symptoms. Because of the progressive nature of HIV infection and development of possible side effects as a result of taking multiple medications, investigating the cause of the patient’s complaints is a difficult task. Therefore, nonspecific symptoms such as nausea, vomiting, or loss of appetite may lead the physician to diagnose serious underlying problems in an HIV-infected patient. We present a case of a diffuse, large B-cell NHL in an HIV-infected woman who has been successfully treated and is a long-time survivor, and we discuss her diagnosis and treatment, as well as review the current literature.

Report of case

A 38-year-old white woman with HIV presented to the hospital in September 1996 complaining of nausea and vomiting of 1 month’s duration, occurring 2 to 3 hours postprandially. She also complained of abdominal pain that would start after ingestion of food and partially resolve with emesis. She denied dysphagia; coffee ground emesis; hematemesis; melena; hematochexia; diarrhea; constipation; fever; chills; hematuria; and tobacco, alcohol, and intravenous drug abuse. She reported anorexia and weight loss over the past year. Her medical history includ-
ed HIV infection for approximately 16 years, which she contracted through blood transfusion. In addition, she had a gastric ulcer diagnosed with endoscopy 4 weeks before admission, which was treated on an outpatient basis with omeprazole and metoclopramide hydrochloride. Her surgical history included cholecystectomy, appendectomy, and total abdominal hysterectomy. Her home medications included clarithromycin, diaminodiphenylsulfone, fluconazole, zidovudine, and lamivudine.

Physical examination revealed a cachectic white woman in no acute distress. She was afebrile, with vital signs as follows: heart rate, 114 beats/min; blood pressure, 104/76 mm Hg; and respiratory rate, 20 breaths/min. Examination of the head, eyes, ears, nose, and throat revealed no abnormalities, and cardiac and pulmonary examinations were within normal limits. Examination of the abdomen revealed diffuse tenderness and diminished bowel sounds. Rectal examination was unremarkable, and hemoccult test result was negative. Laboratory results were normal with the exception of mild leukopenia (white blood cell count, $3.8 \times 10^3/\mu L$) and normocytic anemia. Radiography of the abdomen revealed no obstruction.

Esophagogastroduodenoscopy was performed and showed a large peptic ulcer of the bulb and duodenum. Biopsy from antral mucosa revealed diffuse, large B-cell NHL, based on revised European-American classification of gastric lymphoma in patients with HIV (Figure 1). Magnetic resonance imaging of the brain showed no evidence of tumor involvement. Computed axial tomography of the abdomen and pelvis revealed hepatosplenomegaly, marked thickness of the gastric wall, and hyperemia of the perigastric fat. No ascites or adenopathy were noted. Computed axial tomography of the lumbar spine showed no evidence of fracture or metastatic disease. No evidence of lymphoma was noted. The spinal tap was negative for malignancy. Blood and stool cultures were negative. Herpes simplex virus I and II immunoglobulin G results were positive. Biochemistry profile revealed mild elevation of total protein and globulins. Amylase and lipase were within normal limits.

The chemotherapeutic regimen consisted of cyclophosphamide, $187.5 \text{ mg/m}^2/\text{d}$; doxorubicin, $12.5 \text{ mg/m}^2/\text{d}$; and etoposide, $60 \text{ mg/m}^2/\text{d}$ as a continuous intravenous infusion for 4 days. In addition, cytosine arabinoside (50 mg) via intrathecal injection was used for central nervous system prophylaxis, whereas Sparano and others used methotrexate followed by leucovorine and whole-brain radiation therapy. Prior to initiation of chemotherapy, the patient was empirically started on allopurinol and aggressive intravenous fluid hydration to prevent tumor lysis syndrome. After completion of diagnosis, work-up, and initial treatment, she was discharged with instructions to follow up in a few days for another intrathecal cytosine arabinoside injection, and a regular checkup for evaluation and monitoring of her lymphoma and HIV infection. The overall plan was to complete six cycles of chemotherapy.

Follow-up esophagogastroduodenoscopy showed healed gastric ulcer/lymphoma, deformed antrum, and diffuse gastritis (Figure 2). She completed six cycles of chemotherapy. Her last cycle was in March 1997. She has remained free of symptoms and has been in complete remission approaching 2 years.

Comments

There are many malignancies associated with HIV infection, but NHL has attracted more attention than most among researchers, as demonstrated by numerous published reports. In 1985, the Centers for Disease Control and Prevention revised the definition of AIDS. Accordingly, the CDC included NHL of high pathologic grade (diffuse, undifferentiated) and B-cell or unknown immunologic phenotype as one of the criteria indicative of AIDS (a positive serology for HIV in the absence of the opportunistic disease is required.)
for current case definition). The incidence of NHL related to AIDS has been increasingly recognized. The Table lists several studies of HIV-infected patients with NHL.

Prognosis of HIV patients with NHL is poor. There are several prognostic factors that help to predict survival of such patients. Poor prognostic factors include age greater than 40 years, prior AIDS, beta symptoms, performance status (measure of functional ability) greater than or equal to 2, and CD4 count less than 100/μL.

Treatment of these patients should aim at treating lymphoma and AIDS and their complications. Different chemotherapy regimens have been used for treating NHL with variable results.

Emilie and others used an anti-interleukin monoclonal antibody in such patients. Eleven patients participated in their study. The antibody was administered for 21 days. Lymphoma progressed in five patients during the treatment, growth stabilized in five patients, and partial remission occurred in one patient.

The use of interferon-α and zidovudine has also been reported. In a study of 28 patients with AIDS-related lymphoma, Levin and others used low-dose methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone, with zalcitabine to evaluate the safety of this dual therapy. The authors reported 56% complete remission and noted that such a combination can be administered safely. Sparano and coworkers reported that the use of cyclophosphamide, doxorubicin, and etoposide and filgrastim was as effective in the treatment of patients with HIV-associated NHL and that its use in combination with didanosine was feasible.

Our patient responded well to the chemotherapeutic regimen chosen and is still in complete remission, though she recently returned for hospitalization because of the sudden onset of thrombocytopenia. She was transfused with platelets, and a bone marrow biopsy performed at this time was negative for malignancy or evidence of myelodysplasia. Thrombocytopenia is not infrequent as a complication of systemic chemotherapy or lymphoproliferative malignancies. It was thought that the sudden thrombocytopenia in this patient was due to her dosage of antiretroviral medication, which was adjusted thereafter. Her platelets increased subsequently and have remained within normal range.

The advances in AIDS therapy, the current use of protease inhibitors, and increasing experiences with chemotherapeutic regimens make it reasonable to predict that individuals with AIDS and lymphoma will live longer than has been the case in the recent past. Such patients are, however, always in danger of opportunistic infections. In a case-controlled study, Sparano and others reported a significantly increased risk for serious or

### Table: Selected Studies of HIV-Infected Patients with Non-Hodgkin’s Lymphoma

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<td>Low and high grade (not all cases graded)</td>
<td>20- to 49-year-old unmarried homosexual</td>
<td>1973 to 1984</td>
<td>70% increase NHL among subjects</td>
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<td>High grade (small, noncleaved and large cell, immunoblastic plasmacytoid), 69%; intermediate grade (diffuse large cells), 31%</td>
<td>105 patients with lymphoid neoplasm associated with AIDS</td>
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<td>High grade (aggressive), 62%; subtype intermediate grade, 29%; subtype low grade, 7%</td>
<td>90 homosexual men</td>
<td>Jan 1980 through Dec 1983</td>
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<td>High-grade B-cell lymphoma</td>
<td>84 patients with AIDS-associated NHL</td>
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<td>1086 HIV-infected patients</td>
<td>Jan 1983 through Aug 1995</td>
<td>13 cases of NHL of the gastrointestinal tract and 26 cases of extraintestinal NHL were diagnosed in HIV-infected patients</td>
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fatal opportunistic infections in individuals with HIV-associated NHL due to chemotherapy. The management of these patients is challenging, and chemotherapeutic regimens in conjunction with antiretroviral therapy should be tailored appropriately to each affected individual. The knowledge of the opportunistic infections in such patients needs to be expanded, and more comparative studies of combination antiretroviral and chemotherapeutic regimens need to be conducted. The care of these patients and their potential multiple problems require an ongoing multidisciplinary effort.

References


