Skin disease linked to gadolinium prompts warning

The risk that some patients have for developing a debilitating, life-threatening skin disease linked to the administration of gadolinium calls for close scrutiny of kidney function or even a higher threshold of glomerular filtration rate. Around 400 cases of nephrogenic systemic fibrosis (NSF) have been identified worldwide, and most are related to the administration of gadodiamide (Omniscan, GE Healthcare) in patients with moderate to end-stage kidney disease, according to Prof. Henrik Thomsen, a radiologist at Copenhagen University Hospital in Denmark. Patients with a GFR of <30 mL/min and those on dialysis are at risk, Thomsen said. There also have been reports of patients with a serum creatinine below 2 mg/dL after gadodiamide administration, suggesting that the threshold could be set higher at <60 mL/min. GE Healthcare has posted warnings about gadodiamide in its website. Emily Hayes

AUA new prostate-cancer treatment guidelines

ANAHEIM, CA, May 24, 2007. New guidelines for the treatment of prostate cancer were released on May 21st here at the American Urological Association (AUA) annual meeting. Additional treatment guidelines have been recommended based on consensus of the Prostate Cancer Clinical Guideline Update Panel. Men have a lifetime risk of 3% of dying from prostate cancer, while they have a 17% risk of getting prostate cancer. The previous guidelines have been in effect since 1995. Since then, 2.6 million men have been diagnosed with prostate cancer, and approximately 375,000 men have lost their lives to this disease. One new recommendation is that first-line hormone therapy is seldom indicated for symptomatic patients with more extensive or poorly differentiated tumours whose life expectancy is too short to benefit from treatment with curative intent. Another new recommendation is that the morbidities of androgen deprivation therapy (ADT) should be considered in the context of the existing comorbidities of the patient when choosing palliative ADT. Treatment complications are summarised and analysed in the new guideline, and quality-of-life and treatment decisions are discussed. The role of combined therapy is cited, and future research needs are listed. Randomised, controlled trial results are listed by author and summarised. The 2007 Update of the Guideline for the Management of Clinically Localised Prostate Cancer should be a very helpful tool for physicians in this new era of prostate-cancer treatment. Please visit the link to the 2007 Guidelines at http://www.auanet.org/guidelines

Laura Gater

Sonoelastography makes headway in prostate cancer assessment

Sonoelastography shows strong performance in prostate cancer detection, but room for improvement remains when it comes to specificity, according to research from the Medical University Innsbruck in Austria, a leading center in prostate imaging research. Sonoelastography has been in research stages for many years but has only recently approached the verge of entering clinical practice. The technique uses ultrasound to measure the elastic properties of tissues, based on the well-established principle that malignant tissue is harder than benign tissue. A color classification system registers tissue as benign (green) or malignant (blue). Prostate cancer is one of the most common cancers in men. As diagnostic testing with the prostate-specific antigen blood test has increased, so have the number of biopsies, with a high rate of negative results. Typically, biopsies are performed by urologists guided by gray-scale ultrasound, which suffers from low sensitivity.

The release of two new software upgrades in the last year and the availability of more effective probes have enhanced sonoelastography’s performance in prostate imaging, according to Dr. Ferdinand Frauscher, director of uroradiology at Medical University Innsbruck. „We now have tools that provide better imaging information about tissue elasticity and enable better detection of suspicious lesions,” he said.

At ECR ’07, the Innsbruck researchers presented two new papers about the technique’s role in prostate imaging, based on results with a Hitachi ultrasound system. In the first study, of almost 500 patients, they found a very high correlation between sonoelastography and systematic biopsy results. Patients involved in the study had a PSA level over 1.5 ng/mL and underwent 10-core systematic biopsy. To overcome the challenge of getting adequate compression of the entire gland, the researchers used a narrower region of interest, examining the prostate in three sections: base, midgland, and apex.

According to systematic biopsy results, 125 patients had cancer. There were 321 cancerous areas, with Gleason scores ranging from 3 to 10. Confirmed results on biopsy showed that sonoelastography had very good sensitivity of 86% for the entire prostate organ but lower specificity of 72%. Of 533 findings,
the technique identified 275 false positives, due to mistaken assessments of areas with inflammation and atrophy. Sonoelastography performed best in cancers of the apex, with sensitivity of 79% and specificity of 85% to 93%. Performance of the organ.

“The results are promising, especially in atypical areas,” said Dr. Leo Pallwein, who presented results.

Another study from the same institution suggests sonoelastography can help determine whether cancer has spread beyond the capsule of the prostate gland (extracapsular extension). Making such a determination is crucial for selecting the most appropriate treatment.

Researchers performed sonoelastography and obtained contrast-enhanced T1- and T2-weighted MR images in 15 patients with elevated PSA levels prior to radical prostatectomy. Spectroscopy and image fusion were not performed with MR. Based on the histopathologic results, all cancers were well visualized with both sonoelastography and MRI. Surgery results indicated extracapsular extension in 11 of 15 cases. Sonoelastography showed infiltration of the capsule in eight patients and stiffness in seminal vesicles in four cases. MRI showed infiltration in the perioprostatic fat tissue in seven cases and infiltration of the seminal vesicles in five cases.

“Sonoelastography correlated well with MRI and histologic findings. It showed remarkable strength for prediction of extracapsular extension,” said Dr. Friedrich Aigner, the radiologist who presented the study results.

Emily Hayes

Taken from: Diagnostic Imaging Europe, June-July 2007, p. 6-8.

Stromal invasion as prognosis factors in pT1 micropapillary pattern adenocarcinoma of the lung

Lung cancer is a leading cause of cancer-related deaths in highly industrialized countries of the West. Incidence of adenocarcinoma has permanently been increasing (1). Patients with small adenocarcinomas (<2.0 cm) have good prognosis if there are no distant metastases (2). Such clinical behavior suggests that lung adenocarcinoma is a heterogeneous disease, which has been confirmed by genomic researches. Apart from standard prognostic markers (TNM, pTNM assessment), Kawakami et al. recommend histological evaluation of tumor fibrosis and its invasion into the center of a fibrotic focus (3). Additionally, some authors report that the size of central fibrosis (4), presence of fibroelastic or elastic tissue (5), and desmoplasia proliferation might be reliable prognostic parameters. Stromal invasion grading system has been studied in papillary and micropapillary pattern adenocarcinomas (3). Table 1 shows the relationship between stromal invasion grade and micropapillary pattern. In most cases (68%), invasion grade 3 has been identified and low positivity in other cases. Five-year survival rate for these patients was 63% (Figure 1), which means that patients with micropapillary pattern have poor prognosis. This histological pattern also gives poor prognosis in patients with carcinoma of the breast, bladder, ureter, and parotid gland (6,7). Initial molecular investigations only partially explain the phenomenon of heterogeneity. Genomic investigations of micropapillary pattern-positive cases confirm the loss of the short arm of chromosome 8 (8p) (8). Genes EGFR, TRAIL receptors, DR4, DR5, SCAMI, and prostate specific homeobox gene NKX3A have been mapped in this region. MUC1 expression is also predominantly demonstrated in micropapillary pattern-positive carcinomas of the breast and colon. The expression of this membrane glycoprotein has been correlated to interaction of the cells and stroma or to the metatstazation (3,9).

Table 1. Relationship between grade of stromal invasion and micropapillary pattern

<table>
<thead>
<tr>
<th>Stromal invasion grade</th>
<th>No. of cases</th>
<th>Micropapillary pattern-negative group (%)</th>
<th>Micropapillary pattern-positive group (%)</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>0+ 1+ 2+ 3+</td>
<td>0+ 1+ 2+ 3+</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
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<td>21 (18) 19 (16) 54 (45) 26 (22)</td>
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<tr>
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<td>8</td>
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<td>8 (100) 0 (0) 0 (0) 0 (0)</td>
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<td>21</td>
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<td>7 (33) 6 (29) 7 (33) 1 (5)</td>
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<tr>
<td>Grade 2</td>
<td>10</td>
<td>1 (10) 2 (20) 4 (40) 3 (30)</td>
<td>1 (10) 2 (20) 4 (40) 3 (30)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>81</td>
<td>5 (6) 11 (14) 43 (53) 22 (27)</td>
<td>5 (6) 11 (14) 43 (53) 22 (27)</td>
</tr>
</tbody>
</table>

REFERENCE


Vladimir Balitč

Figure 1. Survival rates of patients with stromal invasion grade 3 carcinomas according to presence or absence of a micropapillary pattern. The prognosis of patients with micropapillary pattern-negative (None and 1+) stromal invasion grade 3 adenocarcinoma was significantly better than those with micropapillary pattern-positive (2+ and 3+) tumors (log rank test, \( P = 0.0196 \) (ref. 3).
Prognostic value of p53 expression in ovarian cancer

Ovarian cancer is the leading cause of death among patients with gynecological cancers. There is no proven method in prevention and often the disease is diagnosed in advanced stage. After surgery, standard treatment modality of ovarian cancer is chemotherapy with taxanes and platinum-based regimens. The only validated marker for ovarian cancer is CA 125, which is detectable in the serum of >90% of women with ovarian carcinomas. CA 125 is, however, reliable only in monitoring response to treatment or disease recurrence and not as a diagnostic or prognostic marker. Therefore, considerable interest lies in identifying molecular prognostic indicators to guide treatment decisions.

A. Psyrri, from Yale Cancer Center in New Haven, Connecticut, and co-workers investigated the prognostic potential of p53 protein expression in 141 patients with ovarian cancer. They measured p53 protein expression using an immunofluorescence-based method of automated in situ quantitative measurement of protein analysis (AQUA).

Protein p53 is regarded as a valuable prognostic marker in cancer with a potential use as a molecular target. A tissue array that composed of 141 advanced stage ovarian cancers uniformly treated was constructed. For evaluation of p53 protein expression, they used immunofluorescence-based method of automated in situ quantitative measurement of protein analysis (AQUA).

They showed as a result that high nuclear p53 expression levels were associated with better outcome for overall survival (OS) (P = 0.0023) and disease-free survival (P = 0.0338) at 5-years. High cytoplasmic p53 expression levels were associated with better outcome for OS (P = 0.0002). In multivariable analysis, high nuclear and high cytoplasmic p53 level with International Federation of Gynecology and Obstetrics (FIGO) stage were the most significant predictor variables for OS and high nuclear p53 level with FIGO stage were the significant predictor variables for disease-free survival.

In conclusion, they point that assessment of the prognostic value of p53 protein levels using conventional immunohistochemistry is limited by the nonquantitative nature of the method. AQUA provides precise estimation of p53 protein levels and is able to elucidate the association of p53 protein levels and ovarian cancer prognosis.

REFERENCE


Aljoša Mandić

Rottlerin enhances imatinib-induced apoptosis

Chronic myeloid leukemia (CML) and about 30% to 40% of acute lymphoblastic leukemia are characterized by reciprocal chromosomal translocations t(9;22), which generates the BCR/ABL fusion gene. The product of this gene is a tyrosine kinase that is constitutively activated and contributes to the proliferation of hematopoietic BCR/ABL+ cells by the activation of various intracellular signaling pathways: Ras, Rap 1, B/Raf, Raf-1, ERK, P13K, STAT 5, and MKK6 (1). Imatinib (STI-571) inhibits the activity of BCR/ABL and thus hinders the proliferation and induces apoptosis of BCR/ABL-expressing leukemic cells in vitro. Imatinib is highly effective in the treatment of CML or Ph chromosome-positive ALL. However, treatment (lasting several months) of the patients with CML or ALL in advanced stages of disease may develop resistance to imatinib due to the appearance of mutations in the BCR/ABL kinase domain. The most frequent mutations are E255K and T315I (2). The existing resistance creates the development of new leukemic clones. To overcome the imatinib resistance new drugs and new treatment strategies are being investigated. ABL inhibitors dasatinib and AMN107 are effective in the treatment of some types of CML but not those that lack T315I mutations (3). Kurouso et al (2007) show that rottlerin synergistically with imatinib induces apoptosis of BCR/ABL leukemia resistant cells. Mechanism of apoptosis is activated through the decline of Δψm mitochondrial membranes; they become less resistant to cytochrome c, which activates caspase-3 and caspase-9 in cytosol and induces apoptotic processes. Pan-caspase inhibitor z-VAD-fmk can only partly inhibit synergic induction of apoptosis by imatinib and rottlerin (Figure 1) (4,5).

Harper JA (2001) suggested a new approach to a safety treatment of CML with mitochondrial uncoupler DNP which FDA prohibited DNA in 1938 because of its side effects (cataract and unexpected deaths). However, investigations of other uncouplers, including UCP-1, UCP-2, and UCP-3 have been initiated with the aim to evaluate their therapeutic potential (5).
REFERENCE


Vladimir Baltić